The New England
Journal of Medicine

VOLUME 209 SEPTEMBER 14, 1933 NUMBER 11

FAT AND THE DIABETIC

BY ELLIOTT P. JOSLIN, M.D.*

INTRODUCTION. So much water has run under the bridge since I wrote "With an excess of fat diabetes begins and from an excess of fat diabetics die, formerly of acidosis, now of arteriosclerosis" that I have felt compelled to look at the problem of Fat and the Diabetic afresh. Certainly fat and the diabetic have claimed a prominent place in our thoughts in the past. In 1914 diabetic coma caused the death of more than half of our diabetics and the relation of fat to its etiology seemed so close that the colored frontispiece of lipemic blood in a diabetic monograph was appropriate. Then we had only dim ideas as to how coma came on and how it should be treated, but today a coma death in diabetes strikes us all as needless and indeed unless actual coma is prevented in our respective communities our consciences convict us of incompetent instruction of our patients. A frontispiece of fat in the blood is just as much needed today and, if its connection with arteriosclerosis likewise could be solved in a decade, how fortunate diabetics would be! Who would have believed that mortality from diabetic coma would drop from 60 per cent to 5 per cent in 17 years. Arteriosclerosis now causes more than half of all diabetic deaths. We cannot expect to lower this mortality to 5 per cent, but I do believe that we should expect in the future to prevent the average diabetic from dying prematurely from this complication.

Our knowledge of the part played by fat in the body both in health and disease has broadened, furnishing new concepts for the treatment of the diabetic patient as well as for an understanding of his disease.

Etiology and Prevention of Diabetes. It is still true that individuals who are fat provide the great majority of our diabetics, and it is probably correct to say that "the individual, overweight, is at least twice, and at some ages 40 times, as liable to the disease", but the fat diabetic does not figure quite so prominently in our eyes as ten years ago.

A decade ago I did not find one diabetic in 2000 whose weight prior to the onset of the disease was 30 per cent below normal, nor did Adams find one in 1000 whose weight had been even as much as 20 per cent below standard. Anders and Jameson similarly found overweight more common among females and Jews—the two groups most prone to diabetes. Today there are three reasons why overweight appears to be and actually is less frequent. First, styles and these times of depression discourage obesity. A second factor is the change among living diabetics in the proportion between the young and the old. Formerly elderly diabetics lived fully five times as long as young diabetics, but today this tendency is reversed and diabetic children are living much longer than adults. In consequence the proportion of young to old diabetics frequenting our offices has greatly increased. Thirdly, diabetics under 35 years of age are not as a rule fat and especially is this true of diabetic children. At the onset of diabetes they are tall rather than fat. Consequently the diabetic parading before us is less conspicuously fat.

However, obesity is still a marked characteristic of the diabetic woman who develops the disease above the age of 45 years. Among my last 4000 diabetics there were 1326 married, widowed or divorced women and their average maximum weight before the disease developed was 181 pounds. There were also 111 single women and their average weight was 161 pounds.

Young diabetics are always teaching us lessons, because in them we find diabetes pure and undefiled. Since children demonstrated that obesity was not a universal causal factor, the influence of heredity began to take on greater significance and children have been the pioneers in showing its importance. At first children presented about the same percentage of diabetic relatives as adults, but now we find that instead of an heredity of 20 per cent, actually 49 per cent of our first 100 children with diabetes of 10 years' duration have diabetic relatives. Moreover, this percentage is an ever-increasing one as time allows more and more opportunity for diabetes to develop and to be discovered among the relatives. While we have observed this growing incidence of diabetic heredity in children, we have discovered it to be increasing in adults. Thus, Priscilla White has found that the diabetic heredity of 100 unselected adult diabetics when first seen in our clinic was 29 per cent, but now that they have been

*Joslin—Director George F. Baker Clinic, New England Deaconess Hospital. For record and address of author see "This Week's Issue," page 560.

restudied after an average interval of five years, 15 new relatives with diabetes have appeared in the group, although not all in new families. This has raised the incidence of heredity from its original 29 per cent to 37 per cent. What will be the incidence of heredity in this group five years from now? If we can only prolong the lives of our patients, there is no doubt but that the influence of heredity will be manifested more and more. With a diabetic heredity proved to exist in half of our cases at the end of ten years of diabetes, we can infer with still more assurance than Naunyn, who recognized in heredity the unifying factor in diabetes, that heredity probably exists in all diabetics. Thus, little by little heredity has displaced adiposity as a cause of diabetes and we can say with Priesel and Wagner that it is not every fat citizen who is prone to diabetes, but only those who are hereditarily predisposed. And these writers' etiological classification of diabetes into the blameless diabetes of the thin tall child and the blameworthy diabetes of the fat adult is helpful. But new vistas keep opening up in the diabetic landscape. Who knows whether a decade hence the tall element in the child may not receive still more attention, because of its suggestion of a pituitary element?

For the present in the etiology and prevention of diabetes the emphasis has shifted from obesity to heredity, from the avoidance of obesity in the multitude to the prevention of obesity in the diabetically predisposed individual. Today we focus on the diabetic family in our endeavor to prevent diabetes. Today we strive to detect it and to prevent it in the families of our patients and we warn them against becoming fat. By concentrating on the diabetic family we make our ammunition many times more effective, because our aim is concentrated.

In our discussions of obesity and its causal relation to diabetes we should remember that it is not so much the actual fat deposited in the body which predisposes to diabetes as it is the process of overeating by which the deposit of fat is acquired. This fact Professor Charles H. Best has impressed upon me. The pancreas of the obese individual may have been overtaxed for years to maintain a normal blood sugar and ultimately have broken down under the strain. There is abundant evidence at hand that the fat individual has a lowered carbohydrate tolerance even though this has not reached the stage of frank diabetes. Opportunity exists here for functional even if not for organic disease of the pancreas. Should the patient have grown fat with fat foods instead of carbohydrate foods, the efficiency of his pancreas may have been lowered just as effectively, because it has long been known that a glucose tolerance test, preceded by a fat diet may present a glycemic curve almost typical of diabetes. Finally in all our thoughts upon diet we must remember the similarity in effect of endogenous fat and exogenous fat. That person who loses weight rapidly is almost invariably living upon a high fat diet, albeit their own human fat, and hence is exposed to all the dangers which an exogenous fat diet entails.

In addition to these physiological reasons is the lack of exercise which adiposity brings. Presumably exercise is as valuable in the prevention of diabetes as in its treatment.

The rapid development of obesity must be distinctly more dangerous than a gradual development, because in a sense it takes the pancreas and other organs concerned in carbohydrate metabolism unprepared. Therefore in our prevention of obesity and perhaps of diabetes we must be on the watch for occasions which lead to rapid increases of weight. Foremost among these are the beginning and ending of the sexual cycle. Particularly important is the ending, because along with advancing age there is less desire to exercise but the habit of eating continues. The metamorphosis taking place in the glands of sex may be a factor too, but it is not necessary now even to conjecture as to their influence. In all conditions accompanied by decrease of exercise one should preach the avoidance of sudden increase of fat. The enforced idleness attending the treatment of fractures, the change of occupation from active outdoor physical work to the confinements of an office desk, such as the change of the police officer from his beat to a headquarters swivel chair, all these changes expose the individual to diabetes. Does the physician to the police in your city warn these men of the dangers of obesity when the type of their job changes? In the recovery from acute infectious diseases, quite apart from the attending impairment of the islands of Langerhans, and still more in the convalescence from disease in the organs neighboring the pancreas, such as the liver and gall bladder, the external biliary ducts, and the duodenum particularly because infectious processes can extend into the pancreas, a diabetic hazard lurks. When you put a strong active man abed because of gastric and duodenal ulcer and then feed him upon cream and eggs and milk, you should have a thought of the amount of weight you are adding to his body and the strain you are throwing on his carbohydrate metabolism handicapped by lack of exercise.

From time immemorial the medical profession has assumed various responsibilities in its contacts with its clientêle—probity, temperance, a moral code above reproach and a discretion which engenders confidence. Mr. Harold Vanderbilt struck a new note when he gave a gymnasium to the medical dormitory of the Harvard Medical School in order that our students should

acquire the habit of protecting their own health during their four years of study and thus grow in physical as well as in medical vigor, thereby setting an example for their adult patients for whom medical progress has done less than for children. It is simply carrying this idea of Mr. Vanderbilt a little farther if doctors would set other examples. They should not be fat and if they have a diabetic heredity they should be doubly cautious in this regard.

Doctors have known of the relation of overweight to diabetes for a good many years. Do doctors acquire blamable diabetes or has their own diabetes been blameless? I was curious to find out. In the *Journal of the American Medical Association* there has been recorded yearly since 1902 the deaths and the causes of death of physicians in the United States. During these 30 years the percentage of diabetic deaths to total deaths among the doctors has risen from about 0.8 per cent to 2.2 per cent. In comparison the percentage of diabetic deaths to total deaths in the registration area of the United States has advanced in equal proportion, namely, from 0.6 to 1.8 per cent which would indicate that the doctors had profited no more from their knowledge of obesity as a cause of diabetes than the laity. In 1932 there were 70 doctors, the highest number yet recorded, who died of diabetes and diabetes ranked eighth in the list of diseases.

In the matter of heredity the laity will look first to the doctor regarding the transmission of the disease to descendants. We should bear in mind that if both parents are diabetic, all the children are likely to have the disease; if one is a diabetic and the other of a diabetic family, half the children theoretically will be diabetic; if neither parent is diabetic but each comes from a diabetic family, one-fourth of the children should acquire it; whereas if a diabetic marries a non-diabetic of a non-diabetic family, none of the children should inherit diabetes.

The Physiology and Pathology of Fat in the Diabetic. New concepts or fresh confirmation of old concepts regarding the rôle of fat in the body and its bearing upon the diabetic have come from the laboratories during the last few years. First of all, I enjoy mentioning a few simple experiments of Rosenfeld[1], published in 1932, because he is a veteran in the diabetic fat campaign. (When this paper was written the very excellent article by Althausen on Dextrose Therapy in Diseases of the Liver had not appeared. *J. A. M. A.*, 100, 1163, 1933.) Normally the fat in the liver is about 10 per cent, but this percentage can be raised to 24 per cent and even 36 per cent by feeding fat exclusively to an animal for four days. Think of it—a liver composed one-fourth to one-third of fat! But this fatty infiltration, extreme as it is, can be prevented or at least reduced to 15 per cent or below by so simple a procedure as feeding carbohydrate along with the fat—eight grams of carbohydrate for each 30 grams fat per kilo body weight. No wonder the surgeons give glucose following operations, because they know that if their patients do not receive food, they simply fall back upon an almost exclusively fat diet composed of their own body fat. As a matter of fact, inanition leads to a greater deposition of fat in the liver than does fat feeding and a few days of fasting has even raised the blood cholesterol by 182 per cent. No wonder that the surgeon gave one of my diabetics, Mrs. H., Case No. 10861, with cancer of the head of the pancreas and obstructive jaundice in the period following choledochogastrostomy 400 grams glucose daily for four days and in this way succeeded in reviving her from biliary coma. Later she tolerated 118 grams carbohydrate without glycosuria. Physiologically one can prevent fatty infiltration of the liver by the simultaneous administration of carbohydrate and conversely from lack of carbohydrate fat collects in that organ. Even the fat liver of phlorhidzin poisoning is prevented if carbohydrate is simultaneously administered orally, but it is not prevented if given intravenously. In Germany during the war-years of undernutrition an increase of diseases of the liver of a serious nature was noted, as for example acute yellow atrophy. This lowered resistance of the liver was considered similar to that of fasting animals whom Roger showed succumbed more readily to poisons than did those animals whose liver glycogen was preserved. Acting on this principle Umber[2] gave large doses of levulose along with insulin to patients with acute yellow atrophy of the liver with the purpose of storing the levulose in the liver as glycogen, and in fact in several instances obtained recovery. Buresch believes their success was not due to simple storage with glycogen, but that thereby material became available out of which new liver cells could be formed, and in fact it should be recalled that such regeneration does take place rapidly. Thus Ponfick and later Eppinger removed three-fourths of the liver from cats and in the course of a few days the defect was remedied and sometimes overdone. Rosenfeld found that the fatty degeneration which takes place in phosphorous poisoning could not be prevented by feeding with carbohydrate unless along with the carbohydrate adrenalin was administered.

It is an odd circumstance that infants withstand the ketosis due to starvation far better than do older children. Is it because that in the intermediary metabolism of infants the glycogen is held more tenaciously and offsets the accumulation of fat which is an accompaniment of starvation? Contrary to the experience of

certain writers, we have found that diabetes in infancy is particularly susceptible to treatment. Or is it because the various fats act differently and that in the diet of infants the character of the fat is more benign?

How can we explain the low fat content in the liver in insulin-treated animals? Does the insulin favor the removal of the fat into other fat depots than the liver either as fat or can it be that it does this through the intermediary stage of glucose? Is the pre-diabetic fat because his constant indulgence in food has led to an overproduction of insulin in order to maintain a normal blood sugar and has thus hurried his carbohydrate into the tissues and transformed it into fat with resulting obesity? One can easily imagine that later the insulin function of the pancreas could become exhausted.

Is the harmful effect of chloroform in diabetes to be explained by the interference with the deposition of glycogen in the liver which is an accompaniment of the use of this drug, thus promoting an increase of fat in the organ?

Fat in the liver varies within a wide range. In normal physiological conditions when the rate of importation of fat is not greater than the rate at which the liver disposes of fat, the liver, like other organs, contains no reserve fat. The normal amount of fat present in the fresh tissue is approximately 3 per cent. In Hershey's and Best's dogs it rose to 35 per cent and in Rosenfeld's experiments with fat feeding to 36 per cent. The highest percentage I have found recorded in a human liver has been 26 per cent and the usual quantity is from 2 to 3 per cent. If we assign a weight to the liver of 1500 grams, the actual quantity of fat which it may contain is normally 30 to 45 grams, although upon occasion it can probably amount to 500 grams. Liver fat is a more highly desaturated fat than fat in muscles or in adipose tissues. Its iodine number is 135 whereas body fat has an iodine number of 65. All over 3 per cent of the fat in the liver is considered to be imported body fat of low iodine number which is there temporarily only. The liver could hardly therefore have accommodated more than half of the two pounds of fat which disappeared from the blood of Rabinowitch's patient in the course of 24 hours.

Glycogen in the liver varies in amount to a far less degree than does fat. Normally in a fasting condition it is present in about one per cent which may *on a rich carbohydrate diet* be raised to 15 per cent. As much as 3.6 per cent glycogen and 18 per cent fat can exist in the liver at one time[3], but in general as one component rises the other falls except when both are present in normal quantities. However, Best, Hershey and Huntsman observed no difference in the quantities of glycogen in the livers of rats heavily infiltrated with fat as compared with those of rats with little fat subsequent to the simultaneous feeding of lecithin. Glycogen in the liver is labile, responds quickly to a variety of influences coming to it from the insulin of the islands of Langerhans, from the glands of internal secretion, pituitary, thyroid, adrenal and either directly or indirectly through these agencies is closely related to the sugar content of the blood. Glycogen in the liver is far more labile than glycogen elsewhere in the body although adrenalin exerts to some extent an influence upon the glycogen in the muscles.

From Toronto and the laboratories of Professor Charles H. Best and his co-workers, Soskin, Hershey and Elinor Huntsman, have recently appeared a whole series of papers which still more intimately connect fat with the diabetic and show its importance in his intermediary metabolism[4]. I will attempt to give you a brief summary of this work.

The life of the depancreatized dog usually ends in one or two weeks. If it receives insulin it can be prolonged and such dogs have lived 11 months although usually for a much shorter period. The diet usually fed these dogs consists approximately of meat 300 grams and sugar 100 grams and a sufficient dose, usually constant, of about ten units of insulin which will allow moderate glycosuria. Death finally ensues with symptoms and signs which are indicative of failure in liver function. The animals grow weaker, the urine becomes scanty and at times contains bile pigments. Glycosuria ceases and toward the very end hypoglycemia has been noted by various observers to occur to such an extent that, although the customary dose of insulin which the animal has received for months is omitted, it persists. If fat is added to the diet of such an animal, the development of these symptoms can be accelerated. In fact, a depancreatized dog finally reaches a stage at which without insulin he can be kept alive and sugar-free for six weeks and then dies with liver intoxication. At autopsy the liver is found filled with fat, even up to 35 per cent, and the iodine number of the fat is comparatively low, 65, showing that desaturation of fatty acids has not taken place.

Conversely, it has been known for years that if raw pancreas is fed to a depancreatized dog along with insulin his life can be prolonged indefinitely.

How does feeding raw pancreas with insulin save the depancreatized animal? Hershey concluded that this was not due to a better assimilation and digestion of fat food brought about by the feeding of pancreas, but that the reason was more subtle and was involved in the intermediary metabolism of fat. He recalled that years ago Bloor had observed that the absence of pancreatic lipase appeared to have no great effect on the hydrolysis of fat in the intestine. Hershey therefore suspected the involvement of some component of fat itself and thought this might be concerned with lecithin. With this in mind he substituted lecithin for pancreas and dogs which were nearly moribund came back to life within a few days, again began to excrete

sugar, and behaved like any depancreatized dogs living on insulin and pancreas.

Lecithin plays an important rôle in the body. In our earliest medical days we always thought of its presence in the brain and recognized that the brain was about the last organ to fail during inanition. Lecithin not only forms a part of the built-in fat of the cell but it is the kind of fat which the cell yields last. Commenting upon the work of Mayer and Schaeffer, Leathes writes: "A picture is presented as it were of the emaciated figure of phospholipins persisting at their post in the starving cell, an immovable part of its protoplasm." With the aid of lecithin fatty acids are transported to the liver and in the liver become desaturated and available for use. In lecithin, therefore, we have a fat which is not inert but evidently performs many functions. We have grown up with the idea that carbohydrate when absorbed from the gastro-intestinal tract passes to the liver and there is converted into glycogen and then discharged as needed into the blood stream. But we must not forget that likewise in the liver take place extensive changes in fat. It is generally accepted that fat is transported to the liver to be desaturated and there prepared for use in the body. In this process the phospholipins (lecithin and cephalin) are all important, serving as an intermediate step and as the end products of the desaturation process. Thus the depancreatized dogs kept alive with insulin but dying subsequently because they were deprived of raw pancreas had livers filled up to 35 per cent with fat with an iodine number of 65.

The Toronto investigators then turned to experiments with rats. They learned that the fatty acids in the livers of rats fed with fat may rise to 18.3 per cent, but if lecithin is added to the fat the average fat in the liver falls to 4.5 per cent. Evidently lecithin prevents the storage of fat in the liver and is an essential agent in the intermediary metabolism of fat. The iodine number of the fat in the liver of the fat fed rats was 100, but in those rats also receiving lecithin was 132.

Then followed many experiments upon dogs and rats with the result that it was demonstrated that neither pancreas nor lecithin was required to keep depancreatized dogs alive, but simply one component of the lecithin, namely choline. And these persistent Canadians did not rest there. Choline is toxic, so they went ahead and later found out that the non-toxic oxidation product of choline, betaine, would act as well as choline itself. And there the matter rests.

Consider the significance of this work. A depancreatized dog—a diabetic dog—can live indefinitely if he is fed meat and sugar and given insulin and raw pancreas, or instead of pancreas, lecithin, or instead of lecithin, choline, or its oxidation product, betaine. Drop the latter and fat accumulates in the liver and pari passu the urine becomes sugar-free and remains so even if insulin itself is now omitted. Chemically the animal is getting better because he is sugar-free, but clinically he is growing worse and in time death suddenly ensues due to hepatic insufficiency. The feeding of fat to these animals in some way led to changes which prevented glucogenesis in the liver, because even the blood sugar was only slightly raised above normal. Evidently there is still much to learn about fat and the diabetic.

Look at this substitution of lecithin for raw pancreas in the diet of these depancreatized dogs from another angle. When lecithin is given the moribund animal, chemically better but clinically worse and not excreting sugar in the urine, he begins to improve and voids urine which contains sugar. From what source does the sugar come? The quantity is greater than could be derived from glycogen and from the protein metabolized. Does it come from the lecithin administered—in other words from fat? Certainly this is a query which many laboratories will strive to answer. As you are aware, in earlier experiments Soskin believed that he demonstrated not only the oxidation of sugar by depancreatized dogs, but also the formation of sugar out of fatty acids. This view was not accepted by Lusk. The question is still in the balance and I think few of us feel capable of deciding on which side is the greater weight of evidence. In general the European school appears to favor the overproduction of sugar from fat and that the pancreas is the regulator of the process and prevents the untimely discharge of sugar from the liver.

Cholesterol. Thus far we have discussed the gross fat in the body and the effects its acquirement might have upon the diabetic state. Reference has also been made to fat in the liver and the peculiar property of lecithin and its component choline in protecting that organ. Now let us turn to a consideration of fat in the blood. Normally it ranges between 1 and 2 per cent but may go up to 25 per cent. In a case of Rabinowitch a pound of fat disappeared from the blood overnight and another pound the next day. Sometimes we can see the gross fat in the blood while at other times the fat is just as much increased and yet it is invisible and we don't know why. Estimations of the fat of the blood are difficult and there are relatively few on record. At the moment I do not recall as comprehensive a series as that made by Horace Gray, then in our Clinic, in 1924. The fat in the blood exists in three forms. 1. Fatty acids free and combined, 2. lecithin to which reference has already been made and 3. cholesterol. Fatty acids constitute the bulk of the fat and as neutral fat I take it represent the bulk of the supposedly inert fat stored in the body as nutritional reserves. Lecithin and its functions have been described. As for cholesterol it is a component which hovers about every living cell in the body. It is a well-defined and

stable chemical substance, universal in its occurrence wherever there are other lipids. It, too, is a vehicle for the transfer of the unsaturated fatty acids in the blood stream.

Cholesterol is the easiest of the fats to analyze. One can determine the percentage of cholesterol in a few cubic centimeters of blood, and of late micro methods are being published by which it can be determined in a fraction of one cubic centimeter. There is another advantage to determinations of cholesterol in that apparently its percentage in the blood varies fairly consistently with the total fat in the blood.

The normal range of cholesterol in the blood is from 125 to 230 milligrams per 100 cc. Within these limits it rises and falls with the fat in the food. It is lowest and shows a most stable value in the fasting state; it reaches a maximum normally at three to four hours after a meal. It, like sugar, varies much in the same individual and a basal value is by no means definite. It falls to extremely low levels in advanced pulmonary tuberculosis and amounted to but 90 milligrams and 68 milligrams respectively in two of our diabetic patients, Case Nos. 2448 and 11471, with tuberculous pneumonia; it is normal or low in hyperthyroidism whereas conversely in hypothyroidism-myxedema—it is distinctly increased and as such is of diagnostic value. In nephrosis it is particularly high and values of 1200 milligrams per cent have been recorded.

The cholesterol in diabetes undergoes wide variations. First of all may I call to your attention trends in values for cholesterol at our clinic over a series of years. Later I will try to explain their significance. (See Table 1.)

TABLE 1

TRENDS IN THE PERCENTAGE OF CHOLESTEROL IN A DIABETIC CLINIC DURING SIXTEEN YEARS

Year	Author	Analyses	Cases	Cholesterol Milligrams in 100 cc. Blood
1916	Bloor			424
1917	Bloor and Gray			385
1924	Gray			290
1927	Hunt			257
1930	Hunt and White	110	children	211
1932	Hunt	1178	children and adults	212

In 1916 Professor Bloor found the average cholesterol of 28 diabetics in our group to be far above normal, 424 milligrams per 100 cc. but by 1932 it was just below the upper limits of normal or 212 milligrams per 100 cc. It should be said, however, that Rabinowitch places the upper limits of normal at 180±. Evidently marked alterations have taken place in our diabetics during this period of sixteen years. This can be illustrated by comparing the classification of the severity of the diabetics in 1916 and today. In 1917 we thought that 44 per cent. of our diabetics were severe, but in 1932 only 3 per cent were placed in such a group. In 1917 we believed 27 per cent of our patients then tested for cholesterol were mild but in 1932 this number had risen to 82 per cent. The above figures represent a cross section of the Clinic only but they do show trends. Even in states of coma we find the cholesterol often lower than formerly and occasionally well within a normal limit. Recently we reported five cases

TABLE 2

CLASSIFICATION OF SEVERITY OF DIABETES AT DIFFERENT EPOCHS BASED UPON THE CHOLESTEROL OF THE BLOOD

Degree of Severity	Year	No. of Cases	Per Cent
Severe			
(Cholesterol 360 or above)	1917	55	44
	1927	12	11
	1932	38	3
Moderate			
(Cholesterol 260-360)	1917	37	29
	1927	19	16
	1932	193	15
Mild			
(Cholesterol 250 or less)	1917	32	27
	1927	85	73
	1932	1028	82

of diabetic coma with CO_2 volume per cent 20 or below with a cholesterol of 130, 156, 124, 161, 184 milligrams respectively and eight cases with average admission cholesterol values of only 270 milligrams per cent.

What is the significance of all this change in cholesterol in the blood from above normal to normal? It is true that our diabetics are living about twice as long as in the earlier period, but mere duration of the diabetes cannot be the reason, because years ago Gray proved that duration of the diabetes was not related to the percentage of cholesterol in the blood, and cholesterol furnishes no evidence to show that diabetes increases in severity the longer it lasts. These values for cholesterol simply mean that the diabetic of today is kept more nearly in a normal state than heretofore and this is plainly obvious from a casual inspection of the appearance and faces of diabetic patients everywhere. All are glad to agree that directly or indirectly this improvement is closely related to the introduction of insulin into the treatment of diabetes, but that is simply a gross answer. Let us examine more in detail other factors which have contributed to bring this about.

The diet of diabetics has altered greatly in the last 16 years. In my own Clinic this is shown by a comparison of the changing values of carbohydrate, protein and fat entering into the diet from 1917 until now. With the decrease of fat from 123 grams to 90 grams and the increase of carbohydrate from 26 to 140 grams all of us can see an explanation of the fall in cholesterol, first, because of the lessened load of

fat heaped upon the liver, just as in the case of the Toronto depancreatized dogs, and, secondly, because like Rosenfeld we have protected the metabolism of fat in the liver by depositing carbohydrate along with it. I would not have you gain the impression, however, that this is the whole story. Years ago, in Ann Arbor, Newburgh and Marsh and Waller showed that providing the total calories of the diet were kept low the diabetic patient could tolerate relatively large quantities of fat, and in 1931 I saw a patient, Case No. 9886, of that Master of Diabetes, Frederick M. Allen, who had lived for 15 years on a low carbohydrate diet, C 60, F 90, F 133 without insulin and yet to my astonishment he showed a normal cholesterol. I urged him to take a higher carbohydrate content of the diet and, if necessary to utilize it, insulin, but he refused because he said he was contented and never missed a day's work. In 1932 I saw him again and his cholesterol was 219 milligrams and his diet unchanged and his condition equally good. Therefore avoidance of overfeeding is a great factor in the prevention of a high cholesterol just as it is in the prevention of diabetes.

Fat is a far more insidious factor in the blood of a diabetic than is sugar. If the sugar in the urine and blood increases, it is reflected in the urine and makes itself known by polydipsia and polyuria. An increase in fat in the blood clinically may escape notice for weeks, months or even years. If the sugar in the blood rises 50 per cent from 100 milligrams to 150 milligrams as it often does after a meal we think nothing of it and even if it doubles to 200 milligrams for the brief interval of one hour many will not even concede that diabetes exists. Apparently in elderly people a high threshold of sugar does little harm although I don't like to see it for fear it will continue to rise. With fat, however, the situation is different and the evidence is growing that a high fat content of the blood presages complications near or remote. What are these complications?

Diabetic coma is the outstanding complication which is usually associated with increased fat in the blood, for convenience recognized and estimated by us chiefly as cholesterol. In all our coma cases in whom the blood has been tested for cholesterol it was high save in five, and therefore these five are of special interest. The coma in these five patients was of short duration and likewise the diabetes. The plasma CO_2 combining power ranged between 12 and 19 volumes per cent. It is worthy of notice that I call your attention only to the cases of coma with a low cholesterol and not to those with high cholesterol values. We have become accustomed to increased fat in coma and are in control of it so that now we pay little attention to it. In my own series since January, 1923, of 221 instances of diabetic coma in 189 patients showing plasma CO_2 combining power of 20 volumes per cent or below, the mortality has been but 13 per cent and in the last 42 cases of the series 5 per cent. One strong reason for this mortality is that 89 of our total coma cases were in children. Among these 89 there was but one mortality.

TABLE 3

THE DIETETIC TREATMENT OF SIX GROUPS OF THIRTY CASES EACH OF DIABETES

Date	Diet in Grams			Calories per Kilogram	Insulin, Units	Age at Onset	Weight in Kilograms	Duration, Years*
	Carbohydrate	Protein	Fat					
1915	26	54	76	18	.....	40	57	9.6
1916	43	60	82	21	.....	46	56	7.7
1917	43	60	90	23	.....	42	54	7.9
1923	71	58	123	34	13	37	53	6.2
1927	96	60	113	28	21	46	59	5.6
1931	144	68	90	32	21	43	58	2.9

*Compiled to July 1, 1927, except for cases seen in 1931.

Coma and a high blood fat usually go together. From these coma cases, however, we have learned that neither the coma nor the high blood fat associated with it is necessarily of very evil prognosis provided there is recovery from the acute emergency. There were 160 of our patients who recovered from coma. Since leaving the hospital there have been 18 who died for one reason or another and the duration of their diabetes as well as the 29 immediately fatal has been fairly respectable, 6.5 years. There still remain 140 coma patients who are living, and already their diabetes is of 6.3 years' duration.

Xanthoma diabeticorum is related to a high blood fat. We have had relatively few cases, but I have never known an instance without the cholesterol being high. Lower the cholesterol and the xanthoma is gone.

With cataracts and arteriosclerosis the connection between high percentages of cholesterol is suspected, but not proved. The best argument in favor of it is this. Among our diabetic children with values for cholesterol above 300 milligrams per 100 cc. blood, these complications are many times as frequent as among those children whose tests for cholesterol are under 230 mg. per 100 cc. blood. But we cannot say from our data that the patient with cataract shows a high cholesterol. In nine of eleven children, however, prior to the discovery of their arteriosclerosis the cholesterol test was

high. The subsequent course of 67 children with high cholesterol tests showed arteriosclerosis was present in 15 per cent, cataract in 8 per cent, nephritis in 6 per cent, one child had tuberculosis and 11 children had pyogenic infections of the skin.

Arteriosclerosis was frequently encountered in young diabetics in 1927. Shepardson[5] studied 50 of my patients who were then under 40 years of age, but had had diabetes for five years or more. Their average age was 23 years and the average duration of the disease was 6.9 years. He found x-ray evidence of arteriosclerosis in 18 or 36 per cent of the number. We know thus far of but three of these patients who have died and now that five years more have elapsed these cases will again be studied and reported upon by Shepardson. Even in these 50 cases, however, Dr. Shepardson observed a striking parallelism between the reduction in average values of blood cholesterols and the reduction in the incidence of arteriosclerosis. He assumes that this parallelism is of definite significance and that the disturbance in fat metabolism resulting from the presence of either untreated or improperly treated diabetes is the pathogenic agent in the formation of arteriosclerosis.

Old arteriosclerotic diabetics as a rule do not exhibit a high blood cholesterol. One cannot claim that the sclerotic plaques in the blood vessels have been deposited because of an increase of cholesterol in the blood. Indeed, in one study made we found that the cholesterol in the blood was lowest in those patients examined who showed the most marked arteriosclerosis. Recently Bloor has found higher values for cholesterol in arteriosclerotic diabetics than in those without sclerosis.

Coincidently with the decrease in coma there has been an increase in deaths from arteriosclerosis. One might be tempted to relate this to disturbance in the metabolism of fat in general and cholesterol in particular, but that is not justifiable as yet. There is another important factor. During this period of the decrease in coma from 60 per cent to 5 per cent and the rise of arteriosclerosis to 62 per cent the average age of my diabetic patients at death upon whom these data are based has risen from 45 years to 62 years. This complicates our problem. Furthermore I suspect that in this period the cholesterol has rather steadily been falling to normal. I certainly cannot connect the incidence of arteriosclerosis with cholesterol as closely as I had hoped. If it is closely connected with cholesterol, then arteriosclerosis may decrease, but even if arteriosclerosis remains stationary at 62 per cent, the average age of my patients at death may advance to such an age that all of them might be expected to show hardening of the arteries.

Low Cholesterol Values in Diabetes. Eighteen diabetics have had cholesterol values below 100. The duration of diabetes at the time of the test varied from 0.2 to 9 years. Ten were females, eight males. Six of the examinations were made in patients who died shortly afterward. Hypoglycemia and normal blood sugar values were the rule, but exceptions occurred.

The conditions in which these low values for cholesterol were found were—infections 6, tuberculosis 3 (2 were fatal), pneumonia 1 (fatal), septicemia 2 (fatal), glandular disease or medication 3, pituitary 2, thyroid 1, pancreatic calculi 1, pernicious anemia 1, unexplained 6. The carbohydrate in the diet varied from 96 to 250 grams and the fat 51 to 146 grams.

The patients had x-ray and pathological evidence of arteriosclerosis in some instances, but we do not know the total cholesterol curve prior to the x-ray. A few had high and later low values.

Cholesterol does not stand in relation to the sugar in the blood. One group of 5 girls showed 398 mgs. blood cholesterol while another group of 5 girls showed 187 milligrams, but the average of the blood sugar was identical, 0.29 per cent in both groups.

A high blood cholesterol I think it is fair to say is reliable evidence that a diabetic is uncontrolled. We feel that the steadily falling to normal of the percentage of cholesterol in the blood coincident with the apparent lessening appearances of severe or at least uncontrolled diabetes is proof of this. We are pleased that today 82 per cent of our children's values for cholesterol are under 230 milligrams per cent. In a way these more normal values make us believe that diabetes is a disease which is largely what the diet and the doctor make it.

The liver is large in many cases of diabetes in children. Dr. White found in 40 per cent of 500 diabetic cases that it was large whereas in the control group of 21 non-diabetic cases only three or 17 per cent had palpable livers. In one patient with an extremely large liver, the liver decreased in size as the cholesterol fell. It was definitely enlarged in a patient whose hypercholesterolemia was most persistent.

In the interpretation of the importance of high and low values of cholesterol in the blood, the factor of time must be considered just as the factor of time is essential in making a diagnosis of renal glycosuria. Between January, 1926 and January, 1933 we have made on 1259 diabetic patients 2771 analyses of blood for cholesterol at the New England Deaconess Hospital. Eventually, and I hope this year, Miss Hunt and Dr. White will report upon the subsequent course of these cases. Suffice it to say now that 61 per cent never showed a value in excess of 230 milligrams per 100 cc. blood. Of the remaining 39 per cent there were 93 cases (80 adults and 13 children), 7 per cent, for whom we have thus far no values under 300 milligrams and 73 cases (42 adults and 31 children), 6 per cent, whose values were above 300

milligrams but have now dropped below 230 milligrams and 24 cases (17 adults and 7 children), 2 per cent, whose values were above 300 milligrams, but are now between 230 and 300 milligrams. The cholesterol in 61 cases (38 adults and 23 children) or 5 per cent has increased. Subsequent data must be sought in all these patients, because only in this way can satisfactory conclusions be obtained.

The Rôle of Fat in the Diabetic Diet. The treatment of diabetes utilizes three major factors, diet, exercise, and insulin. I tell my patients they are charioteers and their chariot is drawn by three steeds whose names are Diet, Exercise, and Insulin, and that they must learn how to manage them, to make them pull together and from day to day as occasion arises distribute the load each must draw. As for the children and their mischievous ponies, none of us must expect too much. At this moment, however, we must confine ourselves to diet and the part in it which fat plays.

In the Naunyn Era, 1898-1914, fat was practically unlimited and the patients were always urged to take more fat. At one time my patients put fat in their soup, their coffee and matched their eggs with portions of fat of equal size. The carbohydrate was kept extraordinarily low with the result that sixty per cent of the cases died of diabetic coma. Yet we must not be too hasty in drawing conclusions; Case No. 8, whose diabetes began at 60, lived out her full life expectancy and so did her sister, Case No. 899 whose diabetes commenced when she was 83 years old. If a diabetic lives as long as his average neighbor that is a triumph. Furthermore, in the Naunyn Era the average diabetic lived 4.8 years which was certainly a gain over his duration in the previous generation. But this is not the whole of the story. There is a remnant of that Naunyn Army of diabetics, a rear guard comprising 10 per cent of the original force, and they are fighting yet, and thanks to them the average duration of the diabetes of the Naunyn period has advanced nearly to seven years. Moreover this has been done on an original ration of fat unlimited, carbohydrate restricted.

Then came the Allen Era, 1914-1922, with control of calories, but carbohydrate low and fat still high. With this simple but fundamental expedient coma as a cause of death fell to 40 per cent and in well-regulated hospitals seldom developed *de novo*. The patients lived longer, originally six years, but the living rear guard of 20 per cent of that Allen Army has enabled it to defend its position so well that the actual duration of the diabetes for this period will reach ten years. Already a considerable number of the original soldiers in this period have won my medal for living longer with the disease than they were expected to live without it.

Now we are living in the Era of Banting and Best, 1922-1932. The discovery of insulin increased the allowance of carbohydrate, decreased the fat in caloric equivalent and besides has steadily increased the total quantity of food which the diabetic receives. Using the yardstick of mortality from coma, we find that immediately it fell to 20 per cent, in the next period of three years to 10 per cent and now among my patients who have died both in the hospital and in their homes, near or remote, to the almost unbelievably low value of 4.8 per cent. Already more than 100 children have survived diabetes ten years. The mortality for diabetes in children is one per hundred per year, and if needless coma were avoided it would be one per hundred every three years. The duration of life of the average diabetic is plainly approaching a normal life expectancy.

Treatment is so successful that it is easy to forget the painful road we have followed to attain it and voices have been raised to allow the diabetic a free diet. But I beg you to remember that only those doctors in the world who dared follow Dr. F. M. Allen and "starved a child to let him live" can have the joy of exhibiting diabetic children who have had the disease more than ten years. Fortunately we do not need to starve a child now, but we must not overfeed any diabetic any more than we would overfeed ourselves.

At present the diet I give my patients is approximately carbohydrate 140 grams, protein 70 grams, fat 90 grams. Children need much more protein and if they require more calories I am inclined to give these calories equally divided between carbohydrate and fat. This diet so far as I can estimate from the remarks of von Noorden[6] in Berlin in December, 1932, is approximately what he recommends. He is authority for the statement that Adlersberg and Porges have receded from their use of extremely high carbohydrate diets and I have noted with satisfaction their observation that the use of such a diet must not be advised wholesale, but rather individualized. Falta[7] likewise has disapproved the reduction to a minimum of so valuable a nutriment as fat. In the *Journal of the American Medical Association* for May 20, 1933 Sansum states that his average carbohydrate for 1931 was 184 grams. From my observation of the children who have been given high carbohydrate and hence of necessity extremely low fat, I know that some give up these diets and prefer a liberal carbohydrate and 75 grams fat or more.

Gratefully and generously do I acknowledge the value of controlling fat and liberalizing carbohydrate and all honor to Sansum, Adlersberg and Porges, Geyelin and Rabinowitch, each of

whom has contributed something new in this dietetic procedure, but I prefer just as I did half a generation ago, when the low carbohydrate, low protein and high fat diets were recommended in Ann Arbor and Lund, Sweden, to proceed slowly, testing each step.

What are our criteria anyway for the treatment of a diabetic today? Health, happiness and chemical assurance in blood and urine that the disease is controlled, the lion caged as the Metropolitan Life Insurance Company puts it. Diabetes is not controlled unless the fat is within normal limits, at least under 230 mgs. per 100 cc. of blood. A blood cholesterol which is 300 mgs. should be viewed with alarm for fear of the immediate or remote consequences. Remember that arteriosclerosis was fifteen times as frequent in our children whose cholesterol was above normal as in the group whose cholesterol was under 230 mgs. Our present diets allow us to keep the cholesterol within the normal zone for 85 per cent of our patients and if rigid adherence to their diets were maintained I suspect it would be normal in all.

However, diabetics are doing extraordinarily well and we must be alert to take advantage of their gains in tolerance for carbohydrate. If they can take more than 140 grams carbohydrate with reasonable doses of insulin, they should receive it.

The chapter of the dietetic treatment of disease is still incomplete. Recall the weird action of lecithin in preserving the life of the depancreatized dog and the use of liver in pernicious anemia.

REFERENCES

1 Rosenfeld, G.: Die Ein- und Ausschaltung der Leber. Arch. f. exper. Path. u. Pharmakol. 166: 205, 1932. Über die physiologische Leberverfettung und deren Verhütung. Arch. f. exper. Path. u. Pharmakol. 166: 211, 1932.
2 Umber, F.: Parenchymschutztherapie bei Leberkranken. Med. Klin. 25: 1578 (Oct. 11) 1929.
3 Foster, G. L., and Benninghoven, C. D.: On fat and glycogen in the tissues in experimentally induced obesity in the rat. J. Biol. Chem. 70: 285 (Oct.) 1926.
4 Best, C. H., and Hershey, J. M.: Further observations on the effects of some component of crude lecithine on depancreatized animals. J. Physiol. 75: 49-55 (May) 1932.
Best, C. H., Hershey, J. M., and Huntsman, M. E.: Effect of lecithine on fat deposition in liver of normal rat. J. Physiol. 75: 56-66 (May) 1932.
Best, C. H., and Huntsman, M. E.: Effects of components of lecithine upon deposition of fat in liver. J. Physiol. 75: 405-412 (Aug.) 1932.
5 Shepardson, H. C.: Arteriosclerosis in a young diabetic patient. Arch. Int. Med. 45: 674-689 (May) 1930.
6 von Noorden, C.: Neuzeitliche Diabetesfragen. Berlin, Urban & Schwarzenberg, 1933.
7 Falta, W.: Discussion. Verhandl. d. Gesellsch. f. Verd.-u. Stoff. 11: 164, 1932.

CARCINOMA OF THE RECTUM AND SIGMOID WITH PARTICULAR REFERENCE TO THE DISEASE AS SEEN IN YOUTH*

BY WILLIAM M. SHEDDEN, M.D.†

IN May, 1931, Mrs. V. H. first presented herself and stated that for the past two years she had noted rectal bleeding. During the past twelve months rectal tenesmus had developed, accompanied by frequent stools sometimes composed of feces, but more often made up of bloody mucus and pus. For the past six months there had been cramps in the lower abdomen, and during her present illness she had lost 42 pounds.

The growth was resected by the abdominoperineal approach and a pathological examination showed it to be an adenocarcinoma with involvement of the regional nodes. Five months later the patient had a metastasis the size of a baseball in the liver, and in nine months was dead.

She had been operated on for hemorrhoids one year and five months after the onset of the bleeding but there is no mention of a rectal digital examination. Was it because she was thirty-three and not in the cancer age? Is there a cancer age?

While it is true that the incidence of malignant epithelial neoplasm in youth is probably under four per cent of the entire incidence of neoplastic disease and that the majority of rectal and sigmoidal cancers occur in middle-aged and elderly subjects, yet the disease not infrequently attacks children and young adults and in the latter group is sufficiently large to be disturbing. Furthermore, it is not at all uncommon for the symptoms to be so atypical that they are unrecognized for a long period, often until there has been an exploratory laparotomy or even an autopsy.

If we are to save any of these young people we must make the diagnosis promptly for it is common to have death supervene in from six months to a year after the onset of symptoms. Only by a routine rectal examination of all patients no matter what their presenting symptoms, will we discover this disease early enough to remove it. Otherwise the growth will usually be found quite inoperable when the patient is first seen. In childhood and to a lesser degree in young adult life it is a fulminating disease. We must not wait for changes in bowel function for, although these are of the gravest importance, many growths are well established before such symptoms develop. We must also recall the fact that rectal bleeding does not always mean "piles" and that "piles" may be associated with rectal or sigmoidal cancer.

Lockhart-Mummery[17] takes a very gloomy view of the prognosis. Five years ago he stated

*From the Surgical Services—Massachusetts General Hospital.

†Shedden—Chief of Rectal Division, Tumor Clinic, Massachusetts General Hospital. For record and address of author see "This Week's Issue," page 560.

that he had no record of any patient under thirty years of age treated for cancer of the rectum who had not died promptly from recurrence, no matter how drastic the operation or other therapy and he questions the value of operation in the case of such individuals.

Though Lynch[19] is not so pessimistic and though he reports five cases of cancer of the rectum between the ages of 20 and 30 who lived for ten years or more, there is no question but that the prospect for a five year surgical cure in a group of patients below the age thirty-five with this disease is markedly less than in a group of patients similarly afflicted and of all ages.

The youngest case of rectal cancer recorded is that of a girl of 11 years reported by Stern[28] in 1892. Stern described the tumor as annular and located 10 cm. from the anus. Under the microscope it was seen to be a "cylindric cell carcinoma". This instance would seem to supplant that of a boy of 13 reported by the Allinghams[2] in 1896 and now a classic.

With reference to malignant tumors of the sigmoid, we have found two cases still younger. These were boys, each aged 9. One was reported by Steiner[27] in 1865. The tumor was described after microscopic examination as an "alveolar epithelial cancer", and was said to be situated in the first portion of the sigmoid. The other was recorded by Leijer[16] in 1872 and was also microscopically verified.

Lasnier[15] has been incorrectly quoted as reporting a child, aged three, with an "epithelioma of the rectum", for a review of his article reveals the fact that he refers to a child of 13.

There is an extraordinary case described by Ahfeld[1] in 1880 of a new-born monster with a tumor at the "termination of the large intestine" and said to be, microscopically, cancer. This case will have to be excluded, however, as the situation of this "termination" is not clear.

TABLE I

CASES COLLECTED BY PHIFER

Our Case No.	Phifer Case No.	Sex and Age	Symptoms	Treatment	Result	Histological Examination
1	5	M 9	Abdominal cramps	Colostomy	Dead	Autopsy alveolar epithelial cancer
2	6	M 9	Ileus	No operation	Dead	Autopsy alveolar epithelial cancer
3	15	M 19	Abdominal cramps Constipation Diarrhea	Colostomy	Dead	Autopsy colloid cancer
4	20	? 18	Constipation Mucous discharge	Colostomy Cautery	Dead	Autopsy gelatinous cylindric cell cancer
5	22	F 17	Rectal bleeding Mucus	Excision	Dead	Autopsy alveolar celled colloid cancer
6	23	F 17	Constipation	Biopsy	Dead	Cylindric cell cancer
7	28	F 11	Ileus	Operated	Dead	Cylindric cell cancer
8	30	M 13	Tumor—during 1½ years	Operated	——	Cylindric epithelial cell cancer
9	31	M 12	Constipation Ileus	Operated	Dead	Autopsy colloid columnar
10	34) 35)	F 12	Abdominal pain Diarrhea	No operation	Dead	Autopsy cylindric cell epithelioma
11	36	M 15	Abdominal pain Bloody stools	Operated	Recovery	Columnar cell cancer
12	37	F 12	Abdominal distention	No operation	Dead	Autopsy colloid cancer
13	38	M 19	Rectal pain Bleeding	Operated	Dead	Cancer
14	39	F 16	Abdominal pain Bloody stools	Biopsy	——	Adenocarcinoma
15	41	M 15	Thought to be intussusception	No operation	Dead	Autopsy alveolar cancer
16	48	M 19	Ileus	Operation	Recovery	Cancer
17	49	M 14	Abdominal pain Bloody discharge	Operation	Recovery	Adenocarcinoma

Nos. 34 and 35 represent not two cases but one; Paultauf and later Zupinger described the same case.

TABLE II

CASES COLLECTED BY BERNOULLI AND AUTHOR

Case No.	Reported by	Sex and Age	Symptoms and Diagnosis	Findings and Treatment	Result	Remarks and Histological Findings
18	Bernoulli, Eug. Inaug. Diss. Bale, 1907.	F 17	Cramplike abd. pains, distention and small frequent stools.	Annular strict. 5 cm. from anus. Colostomy.	Dead 2 days postop.	Carcinomatosis of peritoneum. Perirectal nodes, cancerous. Hist: Cyl. cell cancer.
19	Leijer (quoted by Bernoulli).	F 19	Ileus lower abd. Pain and fever. 5 mos.	Stenosis of rectosigmoid for 7 cm. Rectoperitoneal suppuration. Colostomy.	Dead 9 mos. postop.	Hist: Alveolar ca.
20	Bethe (quoted by Bernoulli).	M 11	"Paraproctal phlegmon."	Ulcer with tuberous edges felt in rectum. No treatment.	Dead soon after admission.	Hist: Ca. primary in rectum metast. in liver and mesenteric and mediastinal glands.
21	Schneider (quoted by Bernoulli).	F 15	Irregular stools 7 increas. pain in anus for 1½ yrs. Passage of blood and pus.	Extensive emaciation. Neoplasm of rectal wall involving vagina. Upper border not accessible.	Further course not given.	Hist: Cyl. cell ca.
22	Luck (quoted by Bernoulli).	F 15	Pain on defecation for 10 wks. Small hemorrhages.	Movable ulcer with hard edges felt 8 cm. from anus posteriorly to the left. Circular resection of rectum by parasacral method.	Not further observed.	Hist: Colloid cancer.
23	De la Camp (quoted by Bernoulli).	M 16	Ileus.	Colostomy.	Dead 10 days post-op.	Hist: Small alveolar ca. Metastases to mesentery and liver.
24	Funke (quoted by Bernoulli).	M 16	Not given.	Circular tumor reaching high in rectum. Sacral glands made out. Extirpation of rectum.	Recurrence from glands and metastases after 4 mos. Dead after 7 mos.	Hist: Colloid ca.
25	Ibid.	F 17	Symptoms (nature not stated). 6 mos. duration.	Circular ulcerated tumor 6 cm. from anus. Sacral glands. Extirpation of rectum.	Dead 3 days postop.	Hist: Colloid ca.
26	Ibid.	M 18	"Troubles with defecation" (stuhlbeschwerden), for 5 wks.	Hard circular tumor palpated 2 cm. from anus. Sacral and iliac glands. Pt. discharged unoperated.	Biopsy showed cancer.	Hist: Colloid ca.

TABLE II (*Concluded*)

CASES COLLECTED BY BERNOULLI AND AUTHOR

Case No.	Reported by	Sex and Age	Symptoms and Diagnosis	Findings and Treatment	Result	Remarks and Histological Findings
27	Ibid.	F 19	"Troubles with defecation" and blood in stools for 2 yrs.	Lower rectum involved in hard tumor mass. High sacral glands. Extirpation of rectum.	Death with peritonitis. No metastases.	Hist: Colloid ca.
28	Kruger (quoted by Bernoulli).	F 19	"Troubles with defecation" for 1½ mos.	Ulcerating tumor of ant. rectal wall above anus. Amputation of 5 cm. piece of rectum.	Discharged incontinent. Dead 2 yrs. later of recurrence.	Hist: Adenoca.
29	Milne (quoted by Bernoulli).	M 12	Abd. pain. Diarrhea.	Ann. growth upper rectum.	Dead day of onset of sympt.	Hist: Colloid carc. (autopsy).
30	Clark, J. H. Ann. Surg., 1926, 84:833.	M 16	Abd. pain.	Ann. stenos, sigmoid growth, colos.	Died 3 days later.	Hist: Adenocarc.
31	Da Costa, J. C. Surg. Clin. N. Am., 1928, 8:691.	M 19	Rectal pain. Consti.	Ann. rectal growth metas. in liver, bladder, pros. glands. Explor op.	———	Hist: Adenoca.
32	Loewenberg, S. A. Med. Jour. & Record, Feb. 15, 1928.	M 18	Diarrhea. Bleeding.	Ba. x-ray. Ca. of sigmoid. Biopsy.	———	Hist: Adenoca.
33	Davis, A. S. Cal. & Western Med., 31:189.	M 14	Abd. pain.	Explor. laparotomy. Ca. rectosigmoid.	———	Hist: Adenoca.
34	Spittler, F. A. Ann. Surg., 88:316.	M 18	Constipation. Bleeding. Abd. and rect. pain.	Explor. lap. Colostomy.	———	Hist: Colloid ca.
35	Fowler, R. H. Med. Record, v. 87:730.	M 15	Abd. and rect. pain. Rectal bleeding.	Hard mass 6 cm. from anus.	Died 1 yr. after onset.	Hist: Adenoca. Autopsy.
36	Shedden, W. M. M. G. H. records, No. 203740.	F 17	Abd. pain.	Distention (abd.). Hard tubular mass 6 cm. from anus. Explor. lap. Colostomy. (D. F. Jones.)	D. 3 mos. later.	Hist: Colloid ca.

In other words, we do not know that the monster had a definite sigmoid, rectum or anus.

This paper includes a group of cases under 20 years of age and another between the ages 20 and 35, for we have found that those under 20 occur so rarely that conclusions drawn from them are not so helpful as in the older series. Jones[12] for instance, in a study of 913 cases of epithelial neoplasms of the rectum found only 0.3% under 18, and Pennington[22] in a review of a still larger series (7174) of cancer of the rectum states that the incidence is only 0.5% in those under the age 20. On the other hand, Lynch[19] records that between the ages 30 and 35 the incidence was 9% of 491 cases of cancer of the rectum and pelvic colon studied by him, and Jacobs[11] mentions 91 cases of rectal cancer in individuals between the ages 31 and 40.

INCIDENCE UNDER AGE 20

Phifer[23] in 1923 collected from the literature 40 cases of carcinoma of the rectum and sigmoid in individuals under 20 years of age. To these he added one of his own, a boy of 19. A review of Phifer's report, however, reveals the fact that in only 17 instances (42%) was there a record of an histological examination of the growth. These 17 I have grouped below for further study.

After a careful search through the literature eighteen more instances of cancer of the rectum and sigmoid in boys and girls under 20 years of age have been found, twelve of which had been collected by Bernoulli. In each instance there has been an histological examination of the tumor. To this group I have added a proved case of malignant neoplasm of the rectum or sigmoid in the above-mentioned age group found in the records of the Massachusetts General Hospital*, making a total of 19. These 19 cases I have appended below in outline form.

If Phifer's and the present groups are combined it is found that there are to date reported 36 cases of cancer of the rectum or sigmoid in individuals under the age of 20. Twenty-two of these were males and 14 females. In one case there is no mention of the sex. The age incidence is as follows:

TABLE III

AGE

Age	No. of Cases
9	2
10	0
11	2
12	4
13	1
14	2
15	5
16	4
17	5
18	4
19	7
20	0

SYMPTOMS

There is apparently a variance between the symptom complex of the youth and that of the adult with cancer of the rectum and sigmoid.

As the growth ulcerates, bleeding is noted. As the tumor increases in size and particularly as secondary inflammation sets in via a surface now denuded of mucosa, pain appears. The irritating presence of this inflamed mass causes tenesmus and frequent stools. As the growth becomes annular and the lumen narrows or as the mass by its bulk blocks the lumen, symptoms of obstruction appear. One must not be misled however, as regards obstruction, by relatively minor symptoms. A patient seen seven months ago illustrates this point. She had been constipated for several years. During the past six months her constipation had increased somewhat but with the aid of two teaspoonfuls of mineral oil a day she was able to have *a good daily bowel movement*. Not until she noticed a slight streaking of blood on her stools did she seek advice. After the sigmoid was resected and the bowel opened a growth was disclosed narrowing the lumen so that it was less than a centimeter in diameter. (See Figure I.)

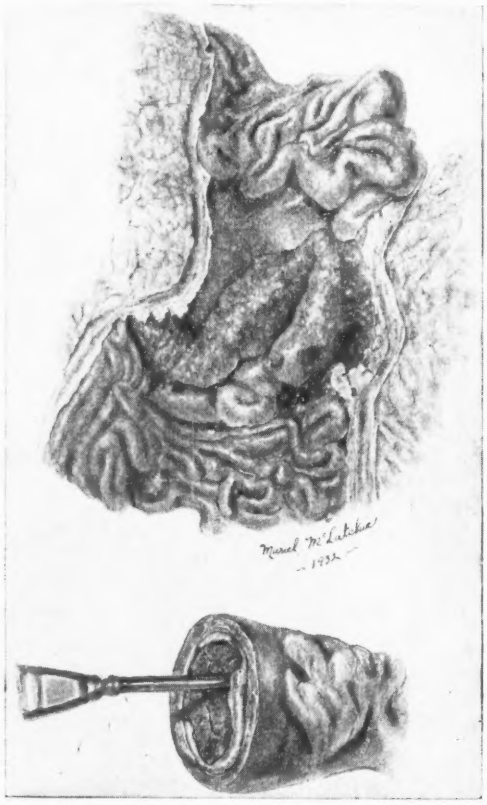


FIG. I. Hartmann Operation.

It will be of interest to recall the symptoms of a group of all ages afflicted with cancer of the rectum or sigmoid. Hayden[10] and I studied a

*I wish to thank Dr. D. F. Jones for permission to review some of his abstract record cards.

series of 303 such cases two years ago. The most frequently recorded symptoms were as follows:

TABLE IV

Symptoms (All Ages)	Per Cent	No. of Cases
Abdominal pain	5	16
Rectal bleeding	64	197
Constipation	50	152
Rectal pain	61	187
Frequent stools	15	47

Let us now compare this table with a tabulation of the symptoms of the youthful group under consideration in this paper. The most frequently recorded symptoms were as follows:

TABLE IV A

Symptoms (Youthful Group)	Per Cent	No. of Cases
Abdominal pain	55	20
Rectal bleeding	30	11
Constipation	30	11
Rectal pain	22	8
Frequent stools	19	7

It will be noticed at once that in the younger group the most frequently recorded symptom is abdominal pain, whereas, in the older group this symptom takes last place. Why abdominal symptoms should predominate over the rectal ones in youth is not clear. It is not reasonable to assume that these youthful patients were less disturbed by rectal sensation than their elders. Were the tumors in the youths at a higher level in the intestine than in the adults and thus more likely to obstruct? Table V shows approximately 33 per cent of the growths in the sigmoid and rectosigmoid. In the groups of all ages abovementioned the comparative figure is 40 per cent.

TABLE V

Level of Growth	No. of Cases
Rectum	20
Sigmoid	11
Rectosigmoid	2
Question whether rectum or sigmoid	3
	36

Was the pain due to abdominal metastases? This is not clear from the reports.

Rectal bleeding is the prominent danger signal in the older group whereas with the children and young adults this symptom is a poor second and on a par with constipation. Does the cancer in the adult tend to ulcerate earlier giving bleeding and rectal symptoms? This also we do not know but it is evident on consideration of the symptoms in youth that their atypicality may blur the diagnosis.

EXAMINATION

It has been stated that there is no disease in which a diagnosis can be made more accurately than cancer of the rectum if the patient is thoroughly examined. Hayden and I found in the series above mentioned that 95 per cent of the growths were within reach of the examining finger. The lesson is obvious; no matter if the patient's story has not the slightest suggestion of cancer of the rectum, a digital rectal examination should always be done. Somewhat over a year ago a patient was seen whose *only symptom was lumbar backache.* History brought out no suggestion of constipation, rectal bleeding, discomfort, mucus, or tenesmus. There was from the examination no suggestion of spinal, renal, or abdominal pathology. X-ray of the spine was negative. Her physician did a rectal digital examination as part of his routine and encountered a growth about 2 cm. in diameter. Biopsy confirmed his suspicions, the tumor being an "adenocarcinoma approaching the colloid type". The growth was resected by the one-stage abdominoperineal technic. The backache gradually disappeared. When seen a month ago there was no recurrence and with such an early removal the patient has excellent prospect for complete cure.

The fact that a patient is disturbed about his rectum or anus should also be sufficient to warrant a thorough examination. These organs, like other viscera, do not intrude into consciousness while they are in a normal state of being. An abnormal sense of anal fullness, a feeling of rectal pressure or heaviness, more than one attack of colic over a short period, all call for investigation. While unexplained anemia is mentioned as frequently resulting from unsuspected growths of the right colon, it must not be forgotten that occasionally a neoplasm of the descending colon may give the same picture.

One way we are going to be able to treat a large percentage of early cases is by instituting a periodic health examination including a digital rectal examination, and an adequate digital examination means one in which the finger sweeps over every portion of the rectum to as high a point as possible. A good-sized carcinoma of the rectum has been missed because it lay in the hollow of the sacrum and the examiner inserted his finger straight past it. If the patient is placed in the so-called left Sims position (lateral decubitus) the finger can usually reach higher than in the knee-chest or knee-shoulder position. Occasionally the squatting position may be required to bring down a prolapsing lesion high up in the rectum or sigmoid. In women the bidigital vaginorectal method may give additional information in the case of a tumor on the anterior wall of the rectum. If there is a suspicion of pathology above the reach of the finger proctoscopy should also

be employed and above that the barium enema.

Proctoscopy or barium enema is necessary in making the diagnosis in some of the sigmoid growths. The diagnosis would have been made by such means in the following case; a man afflicted with considerable urinary retention entered a urological clinic recently. In his past history it is recorded that he had had at times, over many years, obstinate constipation and also occasionally blood in his stools. Rectal examination revealed an enlarged prostate and some hemorrhoids which bled, but no other pathology. Before a prostatectomy could be done he died of pneumonia. Autopsy disclosed besides a moderate hyperplasia of the prostate, "A flat fungating sessile cauliflower almost annular growth of the sigmoid" which on histological examination proved to be colloid carcinoma (figure II).

FIG. II. No. 34. Dr. Shedden. F. C., 320167, March 30, 1932.

Here was a man who had no change in bowel habits over a period of years. Obstinate constipation or rectal bleeding must always suggest malignancy.

Proctoscopy is better done in the knee-chest position as the instrument may be further introduced than in the other positions. It is not within the scope of this paper to go farther into the question of rectosigmoid examination by this method. The reader is referred to an excellent paper by Kleiner[14] for a full discussion of this technic.

It must be remembered that the barium enema is notoriously uncertain in making the diagnosis of cancer within the area between the levels of 20 cm. from the upper border of the anus to the anal opening. In this region a negative barium enema does not rule out cancer.

TABLE VI

DURATION OF DISEASE WHEN FIRST OBSERVED BY PHYSICIAN

(Mentioned in only 7 cases)

Case No.	
19	5 months
22	3 months
25	6 months
26	1 month
27	24 months
28	2 months
29	1 dead

The data on duration of disease before examination by the first physician are so fragmentary in the cases shown in Table VI that no real comparison can be made against older patients. There is no evidence however that delay is a less important factor in the outcome of these cases than it is among adults. Table VII suggests that the physician's advice is not always adequate.

TABLE VII

HOW DISCOVERED

Autopsy	9
Biopsy	4
Laparotomy	19
Unknown	4
	36

These are two of the factors that increase the mortality and lower the operability. But even after the diagnosis has been made there is often a third hurdle to surmount, namely, the patient's, and unfortunately often the physician's, fear of colostomy. In another communication[26] an attempt has been made to show that this fear is ungrounded and that almost every patient can live comfortably, both physically and socially, with a colostomy.

TABLE VIII

TREATMENT (25 CASES)

Colostomy	9
"Operation" (no details)	7
Resection of rectum (no details)	4
Cautery	1
Excision (no details)	1
Parasacral resection	1
Exploratory laparotomy	2
	25

Operative details on these cases are so in-

complete that no judgment as to proper treatment can be formed.

It must be stated however that local excision or cautery has no place in the treatment of cancer of the rectum. In general, proper treatment should be along these lines: when the patient's condition permits, nothing short of a radical resection of the rectum or sigmoid—which usually entails a colostomy—should be advised. Removal of the growth with a good margin of healthy bowel along with the local lymphatic areas that drain it is essential. The technic will vary with the level of the growth. Some form of abdominoperineal operation is to be advised when possible, either the one or two-stage procedure as described by Miles, Jones, Rankin, Coffey, Lahey and others. A method entailing still less risk but with theoretically a greater chance of recurrence is the colostomy and posterior excision advocated by Lockhart-Mummery. This operation is, however, not at all suitable for high growths (i.e., those near the peritoneal reflection). Lockhart-Mummery states that 65 per cent of all cases of carcinoma of the rectum and sigmoid are at or near the rectosigmoid junction but Harrison-Cripps states that the most frequent site is the last three inches. This is the experience of most.

For the sigmoidal growths a resection and end to end suture preceded or followed by a cecostomy, is ideal, but where the growth is lower in the pelvis or the patient is relatively debilitated the technic of Hartmann should be employed. Here the sigmoid is sectioned abdominally well below the tumor. The proximal stump carrying the growth is brought out of the abdomen while the proximal end of the distal stump is turned in. This distal stump may be later removed if it contains polyps. In a large series of rectal cases of all ages and operated by competent surgeons the mortality for the abdominoperineal operation will be about 20 per cent; that for the colostomy and posterior excision will be about 15 per cent. The percentage of patients seen alive at the end of five years after the former operation will be about 30 per cent and after the latter about 15 per cent. These operations have all been clearly described so that we need not go into further detail regarding them.

In over one-third of the operated cases mentioned in Table VIII colostomy only was done. The question of presenting the patient with an abdominal stoma after exploratory laparotomy should be carefully considered. If there is no obstruction and the rectal symptoms are slight many incurable cases should be let alone. The colostomy in these inoperable cases can sometimes be postponed for many months and often be omitted entirely. Rectal discomfort can frequently be better handled by analgesia locally or orally administered.

TABLE IX

RESULTS OF OPERATIVE PROCEDURE

Died immediately postoperatively	5
Died (postoperative life not given)	8
Died—postoperative life 24 months—1 case 9 months—1 case 7 months—1 case 3 months—1 case	4
"Recovered" (no follow-up—type of operation not mentioned)	3
Operative result not mentioned	5
	25

TABLE X

OUTCOME WITH UNTREATED DISEASE (11 CASES)

Died within a few days of examination	2
Died—(no mention of duration of life)	5
Died—(duration—1 year)	1
Outcome not mentioned	3
	11

This table shows that, of the total number, three only were said to have recovered.

When considering untreated cancer of the rectum it is of interest to recall the report of Lazarus-Barlow. He studied 345 instances of untreated cancer of this organ in patients of all ages and found that the average length of life of the males was 20.4 months and of the females 25.9 months. The relatively long duration of untreated rectal cancer must be kept in mind in evaluating the case reports of treated patients who are described as still living two and three years after treatment.

INCIDENCE BETWEEN AGES 20 TO 35

On turning to the young adults afflicted with this disease we find that the incidence is considerably higher. A review of 317 cases of malignant epithelial neoplasm of the rectum operated at the Massachusetts General Hospital between the years 1908 and 1931, reveals that 7 per cent were in this age group. These cases

TABLE XI

AGE AND SEX

There were 18 males and 8 females.
The ages were as follows—

23 — 2
24 — 0
25 — 1
26 — 1
27 — 2
28 — 2
29 — 1
30 — 4
31 — 0
32 — 4
33 — 4
34 — 3
35 — 2

(24 in number) all had a pathological examination of tissue removed at operation, autopsy or biopsy.

FAMILY HISTORY OF CANCER

In only 3 cases was familial cancer recorded (once with a mother, once with a father and once an aunt). It is felt by most of those who have investigated family incidence in studies of cancer of various parts of the body that the frequency of familial cancer is no higher in this disease than in the other diseases.

LOWER LIMIT OF GROWTH

In two instances the growth was said to be not palpable at rectal digital examination. In 21 cases (87%) the growth was within 7 centimeters of the anus (i.e., well within reach of the finger) but in only two instances could it be called small, that is, 1 to 4 centimeters in diameter; the remainder were very large, "filling the rectum", "filling the entire canal", "as large as a billiard ball".

INVOLVEMENT

It has been stated that about a year's time must elapse before a growth becomes annular, but obviously the time element must be modified by the rapidity of growth in the case of the more malignant tumors. In about one-third of the cases the growth was annular. Among the remainder the anterior wall was involved twice as often as the posterior wall.

PREVIOUS TREATMENT

As so frequently happens, several of the patients were delayed from receiving adequate treatment and received cathartics, suppositories, and various forms of hemorrhoid therapy presumably because the diagnosis of cancer was not made.

LOSS OF WEIGHT

Eleven or about half of these patients had definitely lost weight (i.e., ten to thirty pounds) but only two appeared poorly nourished. It is this healthy appearance that may lead one to think that malignancy is not being dealt with. This loss of weight usually, of course, cannot be attributed to the growth per se but usually to loss of appetite. We have all seen hopelessly incurable cases put on weight after a simple exploratory operation. In some cases this is due to the fact that the patient is reassured and as his worry disappears his appetite improves. Others gain weight after a simple colostomy, due probably to the relief of back pressure from partial obstruction and consequent recovery of appetite.

OPERATIVE FINDINGS

Approximately one-fourth of these cases had metastases to regional nodes. In three cases the growth had extended to neighboring intestinal loops, one filled the pelvis, while another had metastasized throughout the abdomen. In only one instance was the liver grossly involved, but obviously because one cannot feel nodules on the surfaces of the liver at operation does not rule out cancer in the depths of that organ. Conversely, nodules in the liver considered grossly to be metastases do not necessarily presage an early death. I have knowledge of one case living four years after such operative findings. This fact is an argument for resection of incurable cases with the purpose of relieving rectal pain.

PATHOLOGY

All of the malignant tumors studied were glandular carcinomata. No squamous cell cancers were seen.

They have been graded relative to their degree of malignancy into malignant adenomata, adenocarcinomata, carcinomata simplex, and colloid carcinomata.

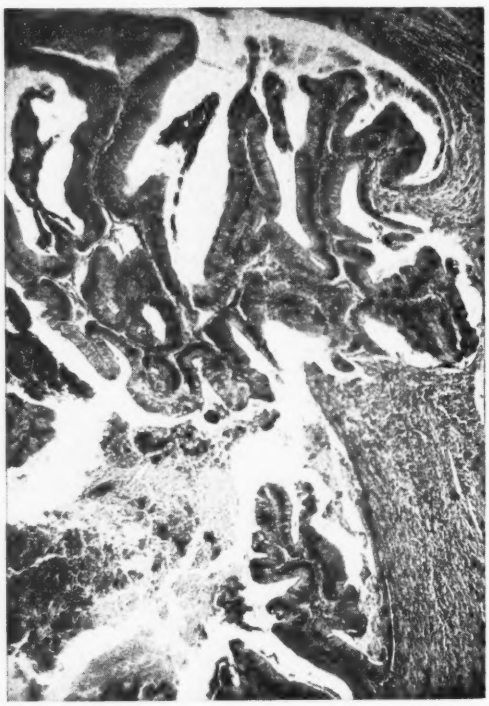


FIG. III. Malignant adenoma. (Magnification approximately 100 ×.)

Shields Warren designates as malignant adenomata (fig. III) those tumors showing large glandular structures similar in size and appearance to benign adenomata and usually derived therefrom but differing in their invasion of the submucosa or sometimes the full thickness of the intestinal wall. These tumors are characterized by a single layer of fairly well-differentiated

epithelial cells and are of a relatively low grade of malignancy.

The adenocarcinomata (fig. IV), show clusters and solid masses of epithelial cells, varying

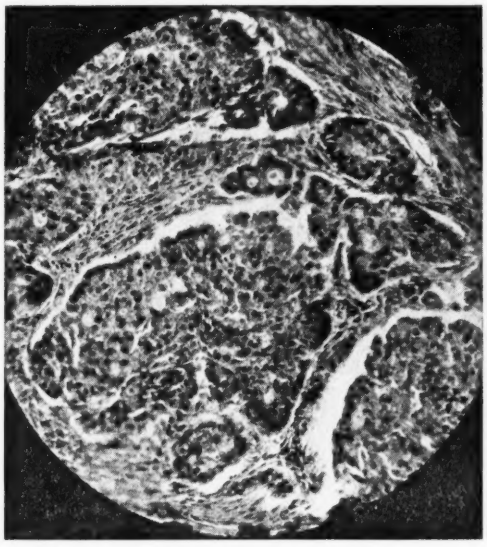


FIG. IV. Adenocarcinoma. (Magnification approximately 100 ×.)

in degree of anaplasia, although associated with the formation of more or less perfect alveoli. These alveoli are frequently smaller than those of the malignant adenoma.

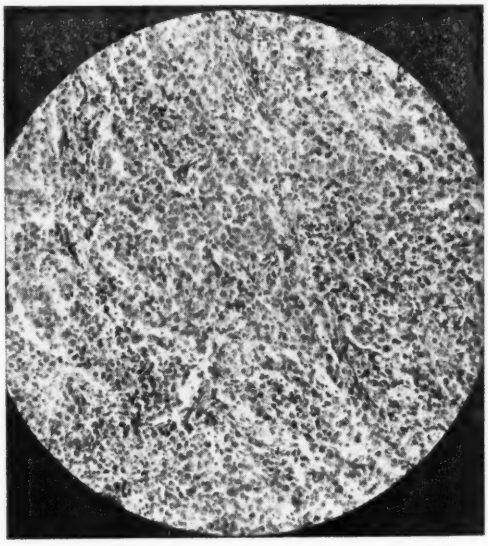


FIG. V. Carcinoma simplex. (Magnification approximately 100 ×.)

In the carcinoma simplex (fig. V), anaplasia is marked and gland formation absent.

The colloid carcinomata (fig. VI), are characterized by an excessive mucoid reaction frequently separating the cells from their stroma. The tumor cells may form poorly outlined glands but often occur in irregular clusters.

In grading, very little emphasis is placed on mitotic figures. The malignant adenoma might be graded I, the adenocarcinoma II, the carcinoma simplex III, and the colloid carcinoma IV.

The tumors in this group of young adults be-

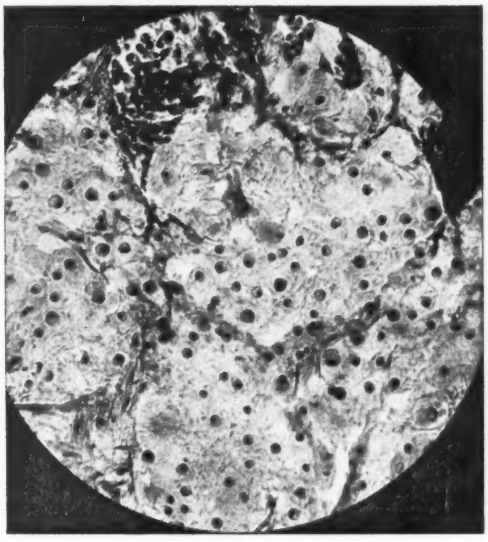


FIG. VI. Colloid carcinoma. (Magnification approximately 100 ×.)

tween the ages of 20 and 35 showed the following microscopic pathology—

TABLE XII

Colloid cancer	3	(12%)
Carcinoma simplex	3	(12%)
Adenocarcinoma	10	(40%)
Malignant adenoma	8	(35%)
	24	

A comparison with the microscopic pathology of the tumors in the youths under 20 is of interest. (See Table XIIIA.)

TABLE XIII

MICROSCOPIC PATHOLOGY

Colloid cancer	11
Adenocarcinoma	8
Cylindric cell cancer	4
Cancer	3
Alveolar cell colloid	2
Alveolar cancer	2
Alveolar epithelial cancer	2
Gelatinous cylindric cell	1
Cylindric cell epithelium	2
Columnar cell cancer	1
	36

When it comes to reviewing the microscopic pathology in these 36 cases we are, of course, compelled to accept the description as given in the case histories as reported and I have given these histological reports just as they appear in the literature. (Table XIII.) The only exception is that of Case 36. Here the pathological section is available for study.

If we were to translate the reports into modern histopathology they would read as follows:

Note that with the youths there is a distinct increase in the most malignant tumors (colloid) and a distinct decrease in the least malignant (malignant adenoma).

The fact that the older the patient the less malignant his tumor tends to be is still more strikingly brought out if we place side by side the microscopic pathology in the youths and that in the group of cases of all ages studied by Hayden and me in 1930.

TABLE XIIIA

Colloid cancer	14	(39%)
Adenocarcinoma	12	(33%)
Malignant adenoma	7	(14%)
"Cancer"	3	
	36	

TABLE XIV

	Youths		All Ages	
Colloid cancer	14	(39%)	1	(1%)
Adenocarcinoma	12	(33%)	30	(34%)
Malignant adenoma	7	(14%)	57	(64%)

If we check the case histories against the microscopic grading as set down in table XII the outcome is quite as one would expect. Of malignant adenomata 43 per cent were living after five years without recurrence. The others died in from 16 to 31 months, the average being 25 months. There is no record of metastasis at the time of operation. Of the adenocarcinomata 20 per cent were living after five years. The others died in from one month to 26 months, the average being nine months. If we add one unusual case that recurred after two years but died only after seven years, the average length of life is brought up to 18 months. Forty-four per cent had metastasized at the time of operation. Of the carcinomata simplex (only two cases) both died, one at eight months and the other at 29 months. There is no record of metastasis at the time of operation. Of the colloid carcinomata (only three cases) all died, one in three, one in eight, and one in 12 months, an average of seven months. There is no record of metastasis at the time of operation.

The prognostic value of this grading depends upon several factors, the most important being a knowledge as to the area of the tumor from which the section under consideration was obtained; for it is recognized that while a section from the surface of the tumor may show "malignant adenoma" of a low grade (fig. VII), that one nearer the base may show one of high grade or an adenocarcinoma (fig. VIII).

A second factor necessary is the knowledge of the actual duration of the disease. There is, of course, a latent period during which the tumor gives no symptoms. This period may vary from several weeks to perhaps several months, depending in great part upon the level of the growth and upon its tendency to ulceration. A tumor near the anus and therefore prone to arouse spasm of the sphincters would, on the chances, give symptoms much earlier than one in the hollow of the sacrum. One often encounters a large tumor with slight or no symptoms at this level. A tumor at the rectosigmoid where the lumen is narrowest tends earlier to obstruct than elsewhere in the rectum. Ulceration of the growth with its accompanying secondary infection gives a distressing tenesmus and thus sounds the alarm.

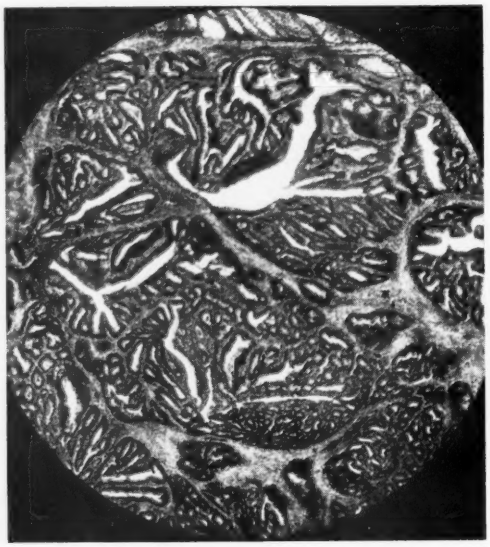


FIG. VII. Two grades—same tumor. A. Malignant adenoma. (Magnification approximately 20 ×.)

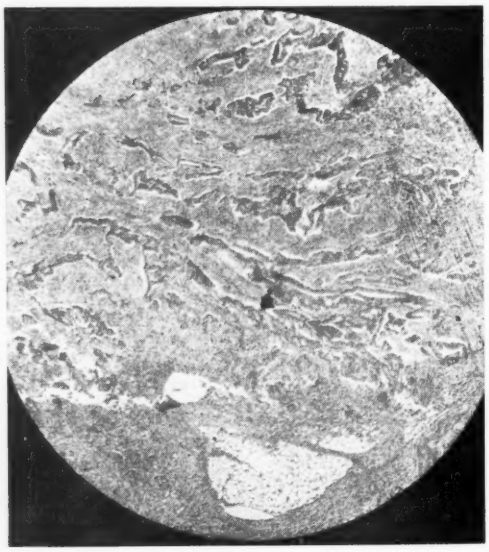


FIG. VIII. Two grades—same tumor. B. Adenocarcinoma. (Magnification approximately 20 ×.)

Thus it can be seen that while the pathological grading might suggest a tumor of low malignancy, yet the level of the growth might delay the onset of symptoms so that by the time the tumor was discovered it might be well advanced

or inoperable. The reverse is also true, that a tumor microscopically highly malignant, might from its level or degree of ulceration give early symptoms and thus be discovered before it had attained a great size.

There is another point regarding the grading of tumors as to their relative malignancy that must be here emphasized, because of its grave possibilities of error in prognosis, and it is this: that, while a section from the tumor near the tip may show a benign tumor, one from the base may show definite malignancy (fig. IX).

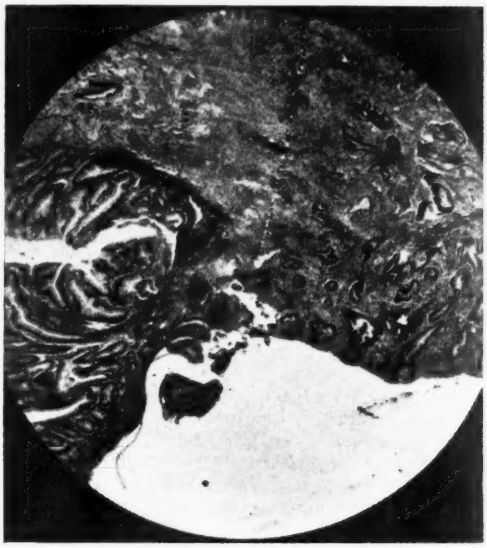


FIG. IX. Transition, polyp to malignant adenoma. (Magnification approximately 20 ×.)

The pathologist must know whence the section comes before giving a final opinion, else he may lull the surgeon to false security with a misleading report. Instead of stating "no malignancy found" it would be better to advise "while no cancer is found in the tissue submitted, a specimen from another part of the tumor may show malignancy". This point cannot be emphasized too strongly. We have twice seen a tumor treated by local measures because of a reassuring pathological report from the biopsy, only to have the growth recur and to find that a definite cancer was present.

It is our feeling that biopsy, by definitely establishing a diagnosis, has advantages that more than outweigh any possible stimulation of the growth by the cutting; for inflamed polyps, lymphomata, and even radium ulcerations may ape carcinoma.

Within two years a rectum was removed and no cancer found by the pathologist. Hard cauliflower-like growths have disappeared after a simple colostomy, leaving only a few tiny adenomatous polyps; obviously the hard mass was an inflammatory tumor. It must be emphasized, however, that a negative pathological report does not exclude cancer. If the clinical appearance and feel of the tumor spell carcinoma to the man accustomed to treating this disease, it is far safer to rely on these criteria than on the biopsy report if the latter is negative.

SUMMARY AND CONCLUSIONS

1. This series embraces 36 cases of cancer of the rectum and sigmoid in individuals under age 20, and 24 cases of the same disease as seen in young adults between 20 and 35.
2. Symptoms in youth may be quite atypical.
3. The younger the patient the greater the tendency to high malignancy.
4. Biopsy for diagnosis, prior to instituting therapy, is always advisable.
5. Watching for change in bowel habits and rectal bleeding, while important, is not enough. Periodic rectal examinations must be made.
6. The therapy of choice is the radical operation; and colostomy, as an adjunct, is always necessary.
7. Pathological grading is apparently of definite value as regards prognosis.
8. Eighty-seven per cent of the rectal and sigmoidal growths in this series were within reach of the finger.

REFERENCES

1 Ahfeld, F.: Zur Casuistik der congenitalen Neoplasmen. Arch. f. Gynäk. 16: 141, 1880.
2 Allingham, W., and Allingham, H. W.: The Diagnosis and Treatment of Diseases of the Rectum. Ed. 6. London, Baillière, Tindall & Cox, 1896.
3 Clark, J. H.: Cancer of sigmoid and rectum in children and young adults. Ann. Surg. 84: 833, 1926.
4 Cutting, R. A.: Carcinoma of the anus and rectum. Am. J. Surg. 10: 547 (Dec.) 1930.
5 Davis, A. S.: Adenocarcinoma in a fourteen year old boy. California & West. Med. 31: 139 (Aug.) 1929.
6 DaCosta, J. C.: Carcinoma of the rectum. S. Clin. N. Amer. 8: 691, 1928.
7 Finney, W. P.: A cancer family. Proc. Staff Meet. Mayo Clinic. 7: 383 (June 29) 1932.
8 Fowler, L. H.: Malignant epithelial neoplasms, carcinoma and epithelioma, occurring in persons under 26 years of age. Surg. Gynec. Obst. 43: 73, 1926.
9 Fowler, R. H.: Carcinoma in the young. M. Rec. 87: 730, 1915.
10 Hayden, E. P., and Shedden, W. M.: Carcinoma of the rectum. Surg. Gynec. Obst. 51: 783, 1930.
11 Jacobs, A. W.: Carcinoma of the rectum and sigmoid. Surg. Gynec. Obst. 43: 50-53, 1926.
12 Jones, D. F.: Carcinoma of rectum. J. Missouri M. A. 24: 179 (May) 1927.
13 Kiger, W. H.: Review of over 300 cases of cancer of the rectum. California & West. Med. 31: 313 (Nov.) 1929.
14 Kleiner, S. B.: Examination of the recto-sigmoidal region. New Eng. J. Med. 203: 870 (Oct. 30) 1930.
15 Lasnier, E. P.: Epithelioma of rectum in child of thirteen. Arch. latino-am. de pediat. 2: 321, 1923.
16 Leijer: Hygeia. 39: 138, 1872.
17 Lockhart-Mummery, J. P.: Prognosis in rectal cancer. Lancet. 2: 1307 (Dec. 25) 1926.
18 Loewenberg, S. A.: Carcinoma of rectum in young man aged 18 years. M. J. & Record. 127: 183 (Feb. 15) 1928.
19 Lynch, J. M.: Cancer of rectum. Surg. Gynec. Obst. 27: 410, 1918.
20 Milne, James A.: Colloid carcinoma at twelve years of age. Brit. M. J. 2: 925 (Oct. 14) 1905.
21 Murdoch, R. L.: Cancer of the rectum; radical and palliative operations—case reports. J. Oklahoma M. A. 21: 241 (Sept.) 1928.
22 Pennington, J. R.: Carcinoma of rectum and pelvic colon. J. A. M. A. 79: 1829 (Nov. 25) 1922.
23 Phifer, C. H.: Cancer of the rectum and sigmoid in childhood and adolescence. Ann. Surg. 77: 711-720, 1923.
24 Rankin, F. W., and Comfort, M. W.: Carcinoma of the rectum in young persons. Collected Papers of Mayo Clinic. 21: 258, 1929.
25 Spittler, F. A.: Carcinoma of the rectum at eighteen years of age. Ann. Surg. 88: 316 (Aug.) 1928.
26 Shedden, W. M.: The management of permanent colostomies. New Eng. J. Med. 206: 792-795 (Apr. 14) 1932.
27 Steiner: Ein Beitrag zu den Stenosen im kindlichen Alter. Jahrb. f. Kinderh. 7: (Heft 2) 59, 1865.
28 Stern, C.: Zur Kenntniss maligner Neubildungen im Kindesalter. Deutsche med. Wchnschr. 18: 494, 1892.
29 Warthin, A. S.: The occurrence of malignant neoplasms in the young. Arch. Int. Med. 15: 444, 1915.
30 Wheeler, W. I. de C.: Early diagnosis of carcinoma of the colon and rectum. Irish. J. M. Sc. P. 579 (Sept.) 1928.

ACQUIRED HYPERSENSITIVITY TO THE ARSENOBENZOL RADICAL OF BISMARSEN*

BY FRANCIS M. THURMON, M.D.,† AND MAURICE M. TOLMAN, M.D.†

BISMARSEN (bismuth arsphenamine sulphonate), a synthetic preparation having an arsenical content of twelve to fifteen per cent and a bismuth content of twenty-three to twenty-five per cent, was introduced by Stokes and Chambers in 1927, when they advocated its use in the treatment of syphilis. Since that time an appraisal of bismarsen in treating various phases of syphilis has been reported by O'Leary, Tobias, Templeton, Montgomery, Elliott, Schoch, Kolmer, Shivers, O'Leary and Brunsting, Hadden and Wilson, and Stokes, Miller and Beerman.

These authors agree in general that the toxicity of bismarsen is low, reactions comparatively benign and controllable, and that it is a useful alternate in cases where other arsphenamine preparations have produced untoward reactions. They do report, however, instances of exfoliative dermatitis, hepatitis with icterus, purpura hemorrhagica (rare), and nitritoid reactions of immediate and delayed types.

The incidence of bismarsen reactions in this clinic is 1.6 per cent. The sixteen cases reported in this communication occurred during the latest one thousand injections of this drug. These patients had previously experienced untoward reactions to the intravenous administration of various arsphenamine preparations before bismarsen therapy was instituted.

Evidence is presented to indicate that these toxic reactions are of a particular type and are due to the arsenobenzol radical contained in arsphenamine, neoarsphenamine, silver arsphenamine, sulpharsphenamine and bismarsen.

The clinical histories of these sixteen cases are summarized in table I. A careful study of these condensed reports reveals one outstanding fact, namely, that regardless of what arsphenamine compound was used the type of toxic reaction was usually the same for that particular patient, and when toxic manifestations to bismarsen occurred, an identical sequence of untoward events took place. This is best illustrated by the case history of a patient that is typically representative of the entire group.

CASE HISTORY

Patient J. M., B. D. No. 270824, a Portuguese male, aged 37 years, entered the clinic November 14, 1927, because of repeatedly positive blood Wassermann reactions. There was no history or clinical evidence of syphilis. The physical examination was negative; the cerebrospinal fluid and urine were normal.

His wife had died with syphilis as a possible cause. Two pregnancies had occurred by this union, the first of which was productive of a still-born child, the second being a full-term babe that lived a day.

Clinical Course—From November, 1927 to September, 1928, he received twenty-seven intramuscular injections of bismuth* and sixteen intravenous injections of arsphenamine without untoward reaction. Ten injections of arsphenamine were then administered and following the tenth he complained of substernal pain. Subsequently he received six injections of neoarsphenamine, ten of bichloridol, twelve of arsphenamine and fifteen of bismuth without ill effect. Then in May, 1930, following the sixth injection of arsphenamine (0.4 Gm.), a mild nitritoid reaction occurred. Twelve bismuth treatments were then administered without toxic reaction. In October, 1930, arsphenamine again caused flushing, dizziness, nausea and vomiting. Later, following the third injection of neoarsphenamine, he developed dizziness, weakness, nausea, chills and fever. Subsequently, twelve intravenous injections of bismuth tartrate (total 0.250 Gm.) were given without toxic reaction. In February, 1932, the second intravenous injection of silver arsphenamine (0.1 Gm.) caused nausea, headache, epigastric pain and malaise. Intramuscular bismuth was then administered without ill effect. In August, 1932, following the third injection of bismarsen (0.2 Gm.) he developed an immediate nitritoid reaction.

The clinical course of the above patient brings out several interesting facts. He manifested nitritoid reactions to arsphenamine, neoarsphenamine, silver arsphenamine and bismarsen. In this respect he is typical of all sixteen cases reported in this communication. They all experienced untoward reactions of one type or another to the various arsphenamine compounds and bismarsen. This fact alone would seem to point to the conclusion that these toxic manifestations were due to some constant factor characteristically present in each of the arsphenamine compounds used, namely the arsenobenzol radical.

In contrast to the toxic manifestations precipitated by arsphenamine compounds, the above patient was able to take bismuth, both intravenously and intramuscularly, and mercury intramuscularly, without manifesting toxic symptoms. Cases 2, 9 and 12, are illustrative of this same point, namely, they received bismuth by intravenous and intramuscular routes without toxic effect, whereas arsphenamine preparations precipitated untoward reactions.

Further evidence to support the view that bismuth was not a causative factor in produc-

*From the Department of Dermatology and Syphilology, and the Division of Research, of the Boston Dispensary.

†Thurmon—Assistant Professor in Dermatology, Tufts College Medical School. Tolman—Assistant in Dermatology and Syphilology, Massachusetts General Hospital. For records and addresses of authors see "This Week's Issue," page 560.

*Bismuth salicylate in doses of 0.130 Gm. each, and iodobismuthate-quinine in 0.170 Gm. amounts, were administered intramuscularly at seven-day intervals.

CHART PRESENTING SIXTEEN CASE HISTORIES
SHOWING TYPES OF UNTOWARD REACT
COMPOUNDS, INCLUDI

Case Histories						*Intravenous*		
Case Number	Hospital Number	Age in Years	Sex	Diagnosis	Period of Treatment	Arsphenamine	Neoarsphenamine	
1	219914	39	Female	Tertiary asymptomatic syphilis.	August, 1922, to October, 1931.	6 inj. Total 1.8 Gm. Nitritoid Reaction 8-30-'23.	1 inj. Amount 0.15 Gm. Nitritoid Reaction 9-4-'29.	12 To No
2	314023	25	Female	Secondary syphilis.	August, 1931, to October, 1931.	7 inj. Total 2.5 Gm. Nitritoid Reaction 9-2-'31.	Seven intravenous total 0.110 Gm., we toward reaction.	
3	316326	43	Female	Tertiary asymptomatic syphilis; Hypertension.	October, 1931, to August, 1932.	4 inj. Total 1.05 Gm. Nitritoid Reaction 4-29-'32.	4 inj. Total 0.75 Gm. Nitritoid Reaction 7-22-'32.	
4	282182	31	Female	Tertiary asymptomatic syphilis; Arrested pulmonary tuberculosis.	January, 1931, to May, 1931.	1 inj. Amount 0.1 Gm. Nitritoid Reaction May, 1931.	3 inj. Total 0.6 Gm. Nitritoid Reaction May, 1931.	
5	277884	43	Female	Tertiary cutaneous syphilis of scalp and forehead.	June, 1928, to September, 1929.	16 inj. Total 5.7 Gm. No Reaction. Poor vein.	3 inj. Total 1.2 Gm. No reaction. Poor vein.	
6	270824	37	Male	Tertiary asymptomatic syphilis.	November, 1927, to August, 1932.	42 inj. Total 12.5 Gm. Nitritoid Reaction 11-22-'30.	9 inj. Total 3.9 Gm. Nitritoid Reactions 12-13-'30, 9-4-'31.	2 i To Ni 2-2
						Twelve intravenous injections of Bismuth Tartr no untoward reaction.		
7	233313	35	Female	Tertiary asymptomatic syphilis; Hypertension.	July, 1924, to December, 1930.	1 inj. Amount 0.2 Gm. Dermatitis 12-20-'24.		
8	185066	30	Female	Gumma of right knee.	February, 1921, to April, 1930.	11 inj. Total 2.4 Gm. No Reaction.		
9	307910	40	Male	Primary syphilis.	February, 1931, to October, 1931.	11 inj. Total 3.9 Gm. Nitritoid Reaction 3-25-'31.	10 inj. Total 4.4 Gm. Nitritoid Reaction 6-2-'31.	
10	242178	52	Female	Tertiary asymptomatic syphilis; Alimentary glycosuria.	April, 1925, to June, 1931.	6 inj. Total 1.6 Gm. Nitritoid and Dermatitis 5-5-'26.	1 inj. Amount 0.15 Gm. Nitritoid Reaction 7-2-'28.	
11	210099	31	Female	Tertiary syphilis of palate; Hyperthyroidism; Aortitis.	January, 1923, to July, 1932.	18 inj. Total 5.4 Gm. Hepatitis and Icterus Feb., 1923. Nitritoid 10-5-'25.		
12	294677	37	Female	Secondary syphilis.	November, 1929, to August, 1932.	32 inj. Total 12.2 Gm. Nitritoids 2-17-'30, 3-24-'30.	12 inj. Total 4.6 Gm. No Reaction.	
13	212163	25	Female	Tertiary syphilis; recently gave birth to congenitally syphilitic child.	November, 1922, to October, 1932.	99 inj. Total 33.6 Gm. Nitritoid 11-15-'28.	9 inj. Total 2.2 Gm. Nitritoid 8-27-'28.	10 To Ni De
14	316957	38	Female	Tertiary asymptomatic syphilis.	December, 1931, to October, 1932.	6 inj. Total 1.6 Gm. Nitritoid Hepatitis Icterus 4-20-'32.	5 inj. Total 2.2 Gm. Nitritoid Reaction 5-25-'32.	
15	202241	41	Female	Tertiary asymptomatic syphilis.	March, 1922, to April, 1931.	21 inj. Total 5.2 Gm. Nitritoids 5-15-'24, 12-27-'28.		4 To Ni 5-2
16	250294	55	Male	Tertiary cutaneous syphilis.	February, 1932, to January, 1933.	14 inj. Total 3.6 Gm. Nitritoid July, 1931.		

*Mercury salicylate and bichloridol were administered at seven-day intervals. The dose of mer

ASE HISTORIES OF PATIENTS TREATED F
OWARD REACTIONS TO VARIOUS ARSPHEN
UNDS, INCLUDING BISMARSEN

—*Intravenous*—		
mine	Silver Arsphenamine	S arsph
	12 inj.	40 inj.
Gm.	Total 3 Gm.	Total 11
ction	No Reaction.	Nitritoi 9-15-'27.

n intravenous injections of Bismuth Tartrate
0.110 Gm., were given without producing ur
rd reaction.

n.
ction

ction

	2 inj.	8 inj.
	Total 0.25 Gm.	Total 3.
ctions	Nitritoid Reaction	No Reac
31.	2-20-'32.	

f Bismuth Tartrate, total 0.250 Gm., produced

1 inj.
Amount
Nitritoi
Dermati

8 inj.
Total 2.
Nitritoi
6-10-'26.

Twenty-one intravenous
were administered, total
ction action.

Gm.
ction

8 inj.
Total 3.
Nitritoi
Dermati
Feb., 19

Five intravenous injecti
0.090 Gm., caused no unt

	10 inj.	4 inj.
	Total 1.7 Gm.	Total 0.
	Nitritoid and	Nitritoi
	Dermatitis 12-1-'30.	5-27-'29.

ction

	4 inj.	18 inj.
	Total 0.6 Gm.	Total 6.
	Nitritoid	Nitritoi
	5-22-'30.	12-31-'25.

. The dose of mercury salicylate varied from 0.020 Gm. t

EATED FOR SYPHILIS,
ARSPHENAMINE

TREATMENT				
	Intramuscular			
Sulph-arsphenamine	Sulph-arsphenamine	Bismuth	Mercury*	Bismarsen
40 inj. Total 11 Gm. Nitritoid Reaction 9-15-'27.		112 inj. Total 14.6 Gm. No Reaction.	42 inj. No Reaction.	1 inj. Amount 0.1 Gm. Nitritoid Reaction 10-19-'31.
Tartrate, ducing un-				1 inj. Amount 0.2 Gm. Nitritoid Reaction 10-31-'31.
		12 inj. Total 1.6 Gm. No Reaction.		3 inj. Total 0.6 Gm. Nitritoid Reaction 8-13-'32.
		10 inj. Total 1.3 Gm. No Reaction.		3 inj. Total 0.3 Gm. Nitritoid Reaction 5-27-'31.
	10 inj. Total 5.7 Gm. Nitritoid Reaction 12-11-'29.	21 inj. Total 4 Gm. No Reaction.	2 inj. No Reaction.	1 inj. Amount 0.2 Gm. Nitritoid Reaction 9-5-'30.
8 inj. Total 3.25 Gm. No Reaction.		66 inj. Total 11.6 Gm. No Reaction.	13 inj. No Reaction.	3 inj. Total 0.6 Gm. Nitritoid Reaction 9-10-'32.
roduced				
1 inj. Amount 0.3 Gm. Nitritoid Reaction Dermatitis 4-15-'29.		92 inj. Total 17.6 Gm. No Reaction.	6 inj. No Reaction.	1 inj. Amount 0.2 Gm. Dermatitis. 12-26-'30.
8 inj. Total 2.4 Gm. Nitritoid 6-10-'26.	1 inj. Amount 0.15 Gm. Nitritoid 12-17-'28.	64 inj. Total 12.8 Gm. No Reaction.	13 inj. No Reaction.	1 inj. Amount 0.1 Gm. Nitritoid 2-24-'30.
ravenous injections of Bismuth Tartrate red, total amount 0.335 Gm., without re-		2 inj. Total 0.26 Gm. No Reaction.		3 inj. Total 0.6 Gm. Nitritoid Reaction 10-21-'31.
		40 inj. Total 6.8 Gm. No Reaction.		1 inj. Amount 0.2 Gm. Nitritoid Reaction 7-25-'31.
8 inj. Total 3.2 Gm. Nitritoid and Dermatitis Feb., 1927.		111 inj. Total 17.2 Gm. No Reaction.		1 inj. Amount 0.2 Gm. Nitritoid and Dermatitis July, 1932.
s injections of Bismuth Tartrate, total d no untoward reaction.		43 inj. Total 0.090 Gm. No Reaction.		1 inj. Amount 0.1 Gm. Nitritoid Reaction 8-1-'32.
4 inj. Total 0.9 Gm. Nitritoid 5-27-'29.		78 inj. Total 13.5 Gm. No Reaction.	7 inj. No Reaction.	1 inj. Amount 0.2 Gm. Nitritoid Reaction 10-1-'32.
		18 inj. Total 2.4 Gm. No Reaction.		1 inj. Amount 0.1 Gm. Nitritoid Reaction 10-26-'32.
18 inj. Total 6.4 Gm. Nitritoid 12-31-'25.	1 inj. Amount 0.2 Gm. Nitritoid 12-23-'26.	53 inj. Total 9.6 Gm. No Reaction.	40 inj. No Reaction.	1 inj. Amount 0.2 Gm. Nitritoid 4-27-'31.
		18 inj. Total 2.3 Gm. No Reaction.		2 inj. Amount 0.4 Gm. Nitritoid 1-12-'33.

0.020 Gm. to 0.060 Gm., while that of bichloridol was 0.133 Gm.

ing toxic reactions is indicated by the fact that, although all of the cases received bismuth intramuscularly, not one of them experienced an untoward manifestation. In contrast to this, each of the arsphenamine compounds used intravenously was capable of producing toxic reactions, and sulpharsphenamine (cases 5, 8 and 15) and bismarsen (all cases) used intramuscularly did likewise.

Evidence to support the view that individual patients manifested a selective type of sensitivity to the arsenobenzol radical may be implied from the fact that when reactions to bismarsen occurred they were similar to the acute and delayed nitritoid crises observed during the administration of other arsphenamine compounds, and when a dermatitis occurred it was of the type associated with arsenical intoxication.

All of these observations indicate that some common sensitizing agent, the arsenobenzol radical, is constantly present in the arsphenamine compounds and bismarsen, and that this portion of these drugs produced a specific type of sensitization and initiated toxic reactions. This statement is in agreement with the findings of Schoch, who, by means of percutaneous tests with potassium bismuth tartrate, concluded that the bismuth content of bismarsen was not the causative factor in producing toxic manifestations.

In general it is agreed that the percentage of untoward reactions to bismarsen is low and that bismarsen is a valuable drug in the therapy of syphilis. Only sixteen patients reacted unfavorably to the drug in a series of one thousand injections. Also, it should be pointed out that, for the most part, our use of bismarsen has been restricted to cases that were unable to tolerate other arsphenamines intravenously, and that the great majority of those patients received bismarsen without manifesting toxic reactions. Therefore, in presenting the above sixteen cases, an attempt has been made merely to call attention to the fact that unfavorable reactions to bismarsen do occur and that these reactions are of a particular type in that they are similar to those observed during the use of other arsphenamine compounds. In other words, when a patient has previously become sensitized to any of the various arsphenamine drugs, that patient retains a potential possibility of manifesting the same type of sensitivity to bismarsen.

In answer to the query that long-continued treatment may have been a factor in producing sensitization, it may be stated that some of the above cases form part of a group being studied to observe the effect of long-continued treatment upon a "serologically-fast" condition, and that within this group those cases manifesting toxic reactions to arsphenamine preparations are comparatively few.

CONCLUSIONS

1. A group of sixteen cases in which bismarsen was used as an alternate drug in the therapy of syphilis because other arsphenamine compounds produced toxic reactions has been presented.
2. Each of these patients manifested the same type of toxicity to bismarsen that was caused by other arsphenamine compounds. The incidence of untoward reactions to bismarsen in this clinic was 1.6 per cent.
3. The data presented indicate that these toxic reactions were due to the arsenical portion of bismarsen and that they were the result of an acquired sensitization to the arsenobenzol radical present in each of the arsphenamine compounds used.
4. In cases that have shown untoward reactions to arsphenamine, neoarsphenamine. silver arsphenamine and sulpharsphenamine, considerable caution should be exercised in the use of bismarsen, because the arsenical content of the latter is sufficient to produce recurrent reactions in these susceptible individuals.

REFERENCES

Stokes, J. H., and Chambers, S. O.: Bismuth arsphenamine sulphonate. J. A. M. A. 89:1500 (Oct. 29) 1927.

O'Leary, P. A.: Bismuth arsphenamine sulphonate. Arch. Dermat. & Syph. 18:372 (Sept.) 1928.

Tobias, N.: Clinical results from the use of bismarsen in tabes dorsalis. Am. J. Syph. 12:536, 1928.

Templeton, H. J.: Bismarsen: an addition in the therapy of syphilis. California & West. Med. 30:55 (Jan.) 1929.

Montgomery, H.: Results in treatment of acute syphilis with bismarsen. Proc. Staff Meet. Mayo Clin. 4:122 (April 17) 1929.

Elliott, J. A.: Bismuth arsphenamine sulphonate. South. M. J. 22:785 (Sept.) 1929.

Schoch, A. G.: Arsphenamine sensitization tests including a report of arsenical dermatitis due to the arsenobenzol radical of bismarsen (bismuth arsphenamine sulphonate). Am. J. Syph. 14:75 (Jan.) 1930.

Ibid.: Systemic reaction to bismarsen. Am. J. Syph. 16:319 (July) 1932.

Kolmer, J. A.: Bismuth arsphenamine sulphonate (bismarsen) in the treatment of syphilis and of other spirochetic infections. Arch. Dermat. & Syph. 21:394 (March) 1930.

Ibid.: Basic bismuth campho-carboxylate (bismo-cymol) in treatment of syphilis. Am. J. Syph. 15:190 (April) 1931.

Shivers, C. H. deT.: The clinical value of bismarsen in the treatment for syphilis. Arch. Dermat. & Syph. 22:462 (Sept.) 1930.

O'Leary, P. A., and Brunsting, L. A.: Further observations on the treatment of acute syphilis with bismuth arsphenamine sulphonate (bismarsen). New York State J. Med. 30:1223 (Oct. 15) 1930.

Hadden, S. B., and Wilson, G.: Bismuth arsphenamine sulphonate (bismarsen) in treatment of tabes dorsalis. Am. J. Syph. 15:316 (July) 1931.

Stokes, J. H., Miller, T. H., and Beerman, H.: An appraisal of the newest arsphenamine synthetic, bismarsen, in the treatment for syphilis. Arch. Dermat. & Syph. 23:624 (April) 1931.

ENDEMIC TYPHUS FEVER IN BOSTON*

A Report of Ten Cases

BY A. CARLTON ERNSTENE, M.D.,† AND JOSEPH E. F. RISEMAN, M.D.†

A MILD form of typhus fever is endemic in the eastern and southeastern parts of the United States[1, 2]. The disease has been observed in Boston, however, only in rare and isolated instances. Lee[3] reported that a diagnosis of typhus fever or Brill's disease had been made in six patients at the Massachusetts General Hospital during the ten years from October 1, 1902, to October 1, 1912, while in twenty-two other patients a condition resembling Brill's disease was observed. Berlin[4] observed three cases of typhus fever at the Boston City Hospital between May, 1914, and July, 1915. Shattuck[5] examined the records of approximately 7000 patients admitted to the Boston City Hospital during the ten years prior to 1922 and found one case in addition to the three reported by Berlin. There were also five probable and five possible instances of the disease. Dameshek[6] observed one case at the Boston City Hospital in 1925. Maxcy[1] mentions six cases occurring in or near Boston between 1918 and 1925. Although a few cases have been observed in other parts of New England[7], these are the only recorded instances of typhus fever in Massachusetts. In view of this low incidence, the fact that ten cases of the disease were observed at the Beth Israel Hospital in Boston during the four year period from 1929 to 1932 inclusive is of considerable interest. During this same four years there were 4,151 medical cases treated in the hospital, an incidence of 2.4 cases of endemic typhus fever per 1000 medical admissions.

Etiology and Epidemiology. Seven of the ten patients were males and three were females; the youngest was 26 and the oldest 60 years of age. All were residents of separated areas of Boston or its suburbs, and all had lived in the United States for many years. In no instance did the disease affect more than one individual in a household. Only two subjects were associated with food handling establishments, and both of these were engaged in the baking industry. No information was obtained as to rat infestation of the houses or places of business of the patients. No lice were found on the person or in the clothes of any subject, nor was a positive history of lice infestation obtained. Two patients were admitted to the hospital in each of the months of May, August, and September; the remaining four were admitted in October, November, January, and February.

Symptoms and Clinical Course. In all patients the diagnosis of typhus fever was based primarily on the clinical features characteristic of the disease, and in eight the clinical diagnosis was substantiated by laboratory tests. A summary of each case is presented in table I. The disease corresponded in all essential details to the condition described by Brill[8] and Maxcy[9]. The onset was always abrupt with fever and general malaise and usually chills and headache. As a rule the patients were severely prostrated and were forced to take to bed within a few hours after the onset of symptoms; four subjects remained ambulatory, however, for one to four days after the appearance of symptoms. Five patients had irregularly recurring chills or periods of chilliness during the first few days of the illness. An unproductive cough was present in six, and one of these also complained of pain in the chest. One patient had mild delirium, one complained of transient diplopia, and one had hiccough for a few days. Three subjects complained of drowsiness; nausea and vomiting occurred in four, and constipation was complained of by five. One patient had epistaxis and another herpes labialis.

All ten patients were admitted to the hospital between the third and eighth day of illness. At that time they appeared acutely ill and severely prostrated and usually were dull and apathetic. They preferred to be left alone and frequently displayed irritation at such interruptions as physical examination and nursing care. Six of the ten patients complained chiefly of headache when first seen, and in two of these stiffness of the neck was noted.

A rash appeared between the sixth and ninth days of illness in every patient. The eruption consisted of irregular, maculopapular, slightly elevated, dull red lesions, one to four millimeters in diameter. When subjected to pressure, the lesions faded but did not disappear. The rash appeared first on the abdomen and lower chest and then usually spread within twenty-four hours to involve the upper thighs, back, chest, shoulders, and neck. In one patient, the eruption extended over the arms, and a few lesions also were noted on the hands. The face was not involved in any subject. The rash usually began to fade within four days after its appearance; in the later stages, the lesions occasionally became hemorrhagic or petechial. The character of the rash and its time of appearance usually were the clinical features which first suggested a diagnosis of typhus fever.

*From the Medical Service, Beth Israel Hospital, the Department of Medicine, Harvard Medical School, and the Department of Medicine, Tufts College Medical School, Boston.

†Ernstene — Assistant in Medicine, Beth Israel Hospital. Riseman—Resident Physician, Beth Israel Hospital. For records and addresses of authors see "This Week's Issue," page 566.

TABLE

SUMMARY OF

Case Number	Age Years	Sex	Admitted to Hospital: Date	Admitted to Hospital: Day of Illness	Symptoms: Fever	Chills	Head-ache	Cough	Miscellaneous Symptoms	Rash Appeared: Day of Illness	Duration: Days	N
1222	49	M	1/17/29	6	+	+	+	0	Vomiting Slight epistaxis Drowsiness	*6	11	
2425	45	F	5/14/29	3	+	+	+	+	Slight sore throat Constipation	7	10	
7949	58	M	8/31/30	7	+	+	0	+	Pain in right chest Constipation	*7	14	
9876	48	F	2/15/31	6	+	+	0	0		9	12	
11877	26	M	8/20/31	8	+	0	+	0	Drowsiness	7	13	
12190	58	M	9/20/31	7	+	+	+	+	Vomiting Constipation Drowsiness	8	21	
12246	60	M	9/27/31	7	+	0	+	+	Constipation Dizziness Slight sore throat Hiccough Transient Diplopia	*7	12	
12735	44	M	11/16/31	8	+	0	+	+	Vomiting Mild delirium Constipation	*8	12	
14686	40	M	5/27/32	8	+	0	+	0	Herpes Labialis	*8	11	
16167	37	F	10/13/32	6	+	0	+	+	Vomiting	*6	11	

*Rash present at time of patie

TABLE I

SUMMARY OF CASES

Rash appeared	Fever			Pulse Rat During Febrile Period
Day of Illness	Duration Days	Maximum Height Degrees F.	Duration of Defervescence Hours	Beats per Minute
*6	11	104.6	48	84-100
7	10	104.5	88	120-130
*7	14	105.0 (R)	88	90-120
9	12	104.2 (R)	96	84-94
7	13	104.0 (R)	56	84-104
8	21	105.0 (R)	108	100-120
*7	12	104.5 (R)	68	100-110
*8	12	104.5 (R)	72	90-112
*8	11	104.0 (R)	44	92-104
*6	11	104.8 (R)	72	88-120

present at time of patient's admission to hospital.

Pulse Rate During Febrile Period	Clinical Pathology							
	Admission Leucocyte Count	*Examination of Spinal Fluid*					*Weil-Felix Reaction*	
		Day of Illness	Initial Pressure	Total Protein Content	Sugar Content	Cell Count	Day of Illness	Agglutination Titer
Beats per Minute	Cells per C.m.m.		M.m. Water	Mg. per 100 Cc.	Mg. per 100 Cc.	Lymphocytes per C.m.m.		
84-100	11,000	6	170	29		6	9	No agglutination
							13	1:20
120-130	7,450						3	No agglutination
							7	1:160
							10	1:500
90-120	4,900						10	1:64
							15	1:128
							29	1:256
							41	1:256
84-94	7,200	10	380	100	68	47	11	No agglutination
		12	200	70		24	23	No agglutination
84-104	6,800	8	220	100	81	18	10	No agglutination
							13	1:50
100-120	8,300						9	No agglutination
							13	1:320
							42	1:200
100-110	9,300	8	70	55	63	7	9	No agglutination
							15	1:50
							27	No agglutination
90-112	12,200	17	40	65	72	8	9	No agglutination
							23	No agglutination
92-104	5,800						12	1:100
							15	1:1000
88-120	13,800						7	1:160
							10	1:640
							13	1:1280
							17	1:640
							21	1:160

UNIV. OF MICH.

The spleen was felt in only one patient.

The pulse rate varied between 90 and 130 beats per minute during the febrile period, the most commonly recorded rate being approximately 100 beats per minute. The respiratory rate was slightly elevated in several subjects.

Fever between 102° and 105° F. was invariably present at the time the patient was admitted to the hospital. In all subjects the maximum temperature was reached on the sixth to tenth day of illness, and, until the beginning of defervescence, only small daily fluctuations in the degree of fever were observed. Defervescence occurred by lysis in one patient. In the other nine the fever terminated by rapid lysis and the temperature reached normal on the tenth to fourteenth day after the onset of symptoms. The onset of defervescence was heralded in six instances by an abrupt rise in temperature to 104° or 105° F. In these subjects defervescence occurred in two distinct stages. The first stage occupied 18 to 24 hours and consisted of an abrupt fall in temperature of three to five degrees succeeded after 4 to 12 hours by a rise of two or three degrees. The minimum temperature attained during this period was 98.6° to 100° F. In the second stage of defervescence, which occupied the following 24 to 48 hours, the temperature fell to a normal level. A typical clinical chart is shown in figure I.

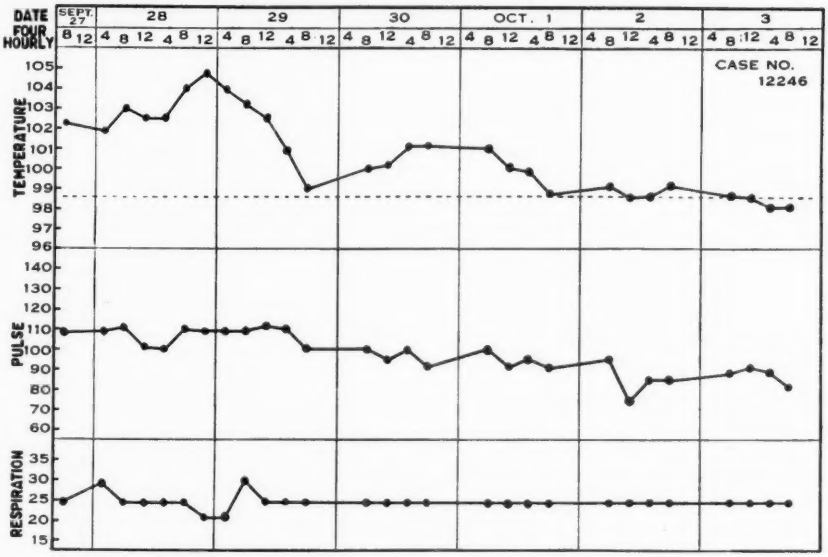


FIGURE I. Typical clinical chart of patient with endemic typhus fever.

With the onset of defervescence, the patients improved rapidly. The headache and other symptoms quickly disappeared, and the period of convalescence was of short duration.

Complications. One patient had transient auricular fibrillation during the febrile period. Two patients presented physical signs and roentgenologic evidence of mild bronchopneumonia toward the end of the illness, and another developed simple parotitis during convalescence.

Clinical Pathology. The erythrocyte count and hemoglobin content of the blood were within the limits of normal in all subjects. At the time of admission, despite the presence of high fever, the white blood cell count was between 4,900 and 9,300 in seven of the ten patients; the highest leucocyte count in the remaining three patients was 13,800. (Table I.) Differential counts of the cells were normal in all subjects. Urinalyses revealed no abnormalities. Cultures of the urine were made in five patients and remained sterile in all. Cultures of the stool were made in eight subjects, and all were negative for pathogenic organisms.

The spinal fluid was examined during the febrile period in five patients. The number of lymphocytes usually was slightly increased, the cell counts ranging from 6 to 47 per cubic millimeter. A moderate increase in the total protein content of the fluid was noticed in four subjects, and in two of these the spinal fluid pressure was elevated.

Agglutination tests for B. typhosus and B. paratyphosus A and B were carried out on the serum of nine patients on at least two occasions and were always negative.

The Weil-Felix agglutination test with B. proteus X-19 was done on at least two occasions in all subjects. In a number of instances, tests on the same specimen of serum were performed in two different laboratories. In five patients there was complete agglutination in a dilution of 1:250 or higher at some time during the period of observation in the hospital. In three other subjects, the test gave negative results at the time of admission to the hospital, but at a subsequent examination there was complete agglutination in dilutions of 1:20 to 1:50. In two patients a positive result was not obtained.

DISCUSSION

The accuracy of the diagnosis of endemic typhus fever in these cases can hardly be doubted. The occurrence of the typical rash in a febrile illness lasting ten to fourteen days constitutes a sufficiently characteristic complex to enable one to recognize the disease on clinical grounds alone. The Weil-Felix agglutination reaction offers confirmatory evidence. The ability of the patient's serum to agglutinate the bacillus proteus X-19 is a phenomenon which, while not specific for this disease, is an almost constant finding and is an important laboratory aid in establishing the diagnosis. According to Maxcy[9] the Weil-Felix reaction makes its appearance late in the disease and is practically always positive in endemic typhus fever if blood is taken at the proper time or if repeated tests are made. In eight of the ten cases seen at the Beth Israel Hospital the clinical diagnosis was substantiated by the results of the Weil-Felix reaction. In five of these cases the reaction was negative at the time of admission, only to become positive later in the course of the disease. More frequent repetition of the test in the remaining two subjects would presumably have resulted in a positive test being obtained.

Endemic typhus fever is to be differentiated from epidemic typhus fever and Rocky Mountain spotted fever[10]. The Weil-Felix reaction may be positive in all of these diseases, but the three conditions can be differentiated on clinical and epidemiologic grounds. Instances of epidemic typhus fever have been observed but rarely in the United States and then only in connection with recently arrived immigrants[10]. The disease is highly communicable, is transmitted from man to man by infected body lice, and tends to occur in widespread epidemics. It attains its maximum incidence during the winter months and is associated with uncleanliness and overcrowding in households, jails, hospitals, and military camps. As a rule, it is a much more severe illness than endemic typhus fever, although mild cases are seen during inter-epidemic periods[9]. The mortality rate in epidemic typhus fever, although variable, is usually considerable.

In contradistinction to epidemic typhus fever, endemic typhus fever, or Brill's disease, is not a louse-borne disease, and multiple cases in households or other places where people congregate are rare. The disease rarely causes death. In contrast to the winter prevalence of epidemic typhus, the endemic form attains its maximum incidence in the summer and fall months. All available evidence indicates that infected rats act as the reservoir in which endemic typhus is kept alive and that the disease is carried from rat to man by rat fleas[11]. A number of the recorded cases of the disease have occurred in the vicinity of food handling establishments that were infested with rats[10]. Unfortunately, we were unable to obtain definite information as to rat infestation of the homes or places of business of our patients. It may be of significance, however, that two of the subjects were associated with the baking industry.

Although Rocky Mountain spotted fever has occurred in the Eastern states in recent years[2], cases have not been observed thus far in New England. The disease differs from endemic typhus fever both clinically and epidemiologically. Whereas endemic typhus fever occurs predominantly in city dwellers, the eastern cases of Rocky Mountain spotted fever have been observed in patients from rural sections or having rural contacts. As a rule, there has been no association with rat-infested premises, and usually there has been a history either of recent tick bite or of having crushed engorged ticks removed from domestic animals[10]. According to Dyer and his associates[10], the fever in the eastern variety of Rocky Mountain spotted fever usually lasts for a longer time than in endemic typhus fever. The rash, as a rule, appears first on the wrists and ankles and much more frequently becomes petechial or purpuric in its later stages. The spleen is much more commonly enlarged, and nervous and mental symptoms are more severe. In contrast to the exceedingly low mortality rate in endemic typhus fever, the observed cases of eastern Rocky Mountain spotted fever have been attended by a mortality of approximately 23 per cent. There were no epidemiological or clinical features in our cases to indicate the presence of Rocky Mountain spotted fever rather than endemic typhus.

The presence of a slight elevation in the total protein content and number of lymphocytes in the spinal fluid in several of our patients is of interest in connection with the prominence of headache, lethargy, restlessness and irritability as symptoms of the disease and the occasional presence of stiffness of the neck. Brill[8] and Maxcy[9] also observed an increased number of cells in the spinal fluid of patients with endemic typhus. Although the pathologic changes in the central nervous system in epidemic typhus have been thoroughly studied[12], we have been unable to find recorded observations on the brain and spinal cord of patients dying of endemic typhus fever. In view of the symptoms referable to the nervous system, the changes in the spinal fluid, and the fact that the virus of endemic typhus can be recovered from the brains of infected laboratory animals, it seems probable that lesions somewhat similar to those of epidemic typhus are present in the nervous system of patients with endemic typhus fever.

The fact that ten cases of endemic typhus fever were seen at the Beth Israel Hospital during a period of four years indicates that there is a rather widespread reservoir of the disease in and about Boston. It also suggests, in view of the small number of cases hitherto reported,

that unrecognized instances of endemic typhus are occurring in the community. The present communication is submitted with the hope that it may be of aid in the diagnosis of future cases.

SUMMARY

1. Ten cases of endemic typhus fever were observed at the Beth Israel Hospital in Boston in the four years from 1929 to 1932 inclusive.
2. The disease corresponded in all essential details to the condition originally described by Brill, and known as Brill's disease.
3. All the patients were residents of separated areas of Boston or its suburbs, and all had lived in the United States for many years.
4. In no instance did the disease affect more than one individual in a household.
5. Six of the ten cases occurred during the warmer months of the year.
6. A positive Weil-Felix agglutination reaction was obtained with the serum of eight of the ten patients.
7. In several of the subjects a slight elevation in the total protein content and number of lymphocytes in the spinal fluid was observed during the febrile period.
8. The differential diagnosis of endemic typhus fever, epidemic typhus fever, and the eastern variety of Rocky Mountain spotted fever is discussed.
9. The fact that ten cases of endemic typhus fever were diagnosed at the Beth Israel Hospital during a period of four years indicates that there is a rather widespread reservoir of the disease in and about Boston, and suggests that unrecognized instances of the disease are occurring in the community.

REFERENCES

1 Maxcy, K. F.: The distribution of endemic typhus (Brill's disease) in the United States. Pub. Health Rep. 43²: 3084 (Nov. 23) 1928.
2 Rumreich, A., Dyer, R. E., and Badger, L. F.: The Typhus-Rocky Mountain Spotted Fever group; an epidemiological and clinical study in the eastern and southeastern states. Pub. Health Rep. 46¹:470 (Feb. 27) 1931.
3 Lee, R. I.: Typhus fever (Brill's disease) at the Massachusetts General Hospital in ten years (Oct. 1, 1902 to Oct. 1, 1912). Boston M. & S. J. 168:122 (Jan. 23) 1913.
4 Berlin, M. G.: A report of three cases of typhus fever. Boston M. & S. J. 175:755 (Nov. 23) 1916.
5 Shattuck, G. C.: Typhus fever at the Boston City Hospital. Boston M. & S. J. 186:235 (Feb. 23) 1922.
6 Dameshek, W.: Typhus fever—report of a case. Boston M. & S. J. 193:260 (Aug. 6) 1925.
7 Blumer, G.: The occurrence of undulant fever and typhus fever in Connecticut. New Eng. J. Med. 200:215 (Jan. 31) 1929.
8 Brill, N. E.: An acute infectious disease of unknown origin; a clinical study based on 221 cases. Am. J. M. Sc. 139:484 1910.
9 Maxcy, K. F.: Clinical observations on endemic typhus (Brill's disease) in southern United States. Pub. Health Rep. 41¹:1213 (June 18) 1926.
10 Dyer, R. E., Rumreich, A., and Badger, L. F.: The Typhus-Rocky Mountain Spotted Fever group in the United States. J. A. M. A. 97:589 (Aug. 29) 1931.
11 Dyer, R. E., Badger, L. F., Ceder, E. T., and Workman, W. G.: Endemic typhus fever of the United States; history, epidemiology and mode of transmission. J. A. M. A. 99:795 (Sept. 3) 1932.
12 Wolbach, S. B., Todd, J. L., and Palfrey, F. W.: The etiology and pathology of typhus. The main report of the Typhus Research Commission of the League of Red Cross Societies to Poland. Cambridge, Harvard University Press, 1922.

FAMILIAL CONGENITAL DISLOCATION OF THE HIP*

BY S. S. HANFLIG, M.D.†

THE pathogenesis of congenital dislocation of the hip is uncertain and mostly speculative. Various theories have been advanced, and, to substantiate these evidence of various sorts has been presented.

That theory of pathogenesis which has seemed to be the most likely for most cases has been the mechanical theory. According to this concept, the dislocation is considered to be the result of chronic trauma to which the lower limbs and consequently the hip joints of the fetus are exposed in the second half of prenatal life. The flexion and external rotation of the lower limbs of the fetus, the lack of proportion which physiologically exists between the femoral head and the socket, the softness of the rim of the socket, and the physiological anteversion of the neck of the femur, all favor a dislocation which manifests itself at birth, as the limbs pass from flexion to extension.

This concept does not explain every case. In many instances an hereditary factor must be inferred and the origin of the deformity must be traced beyond any mechanical cause. We must rather assume that the dislocation is induced by atypical morphological conditions which can be transmitted from one generation to the next.

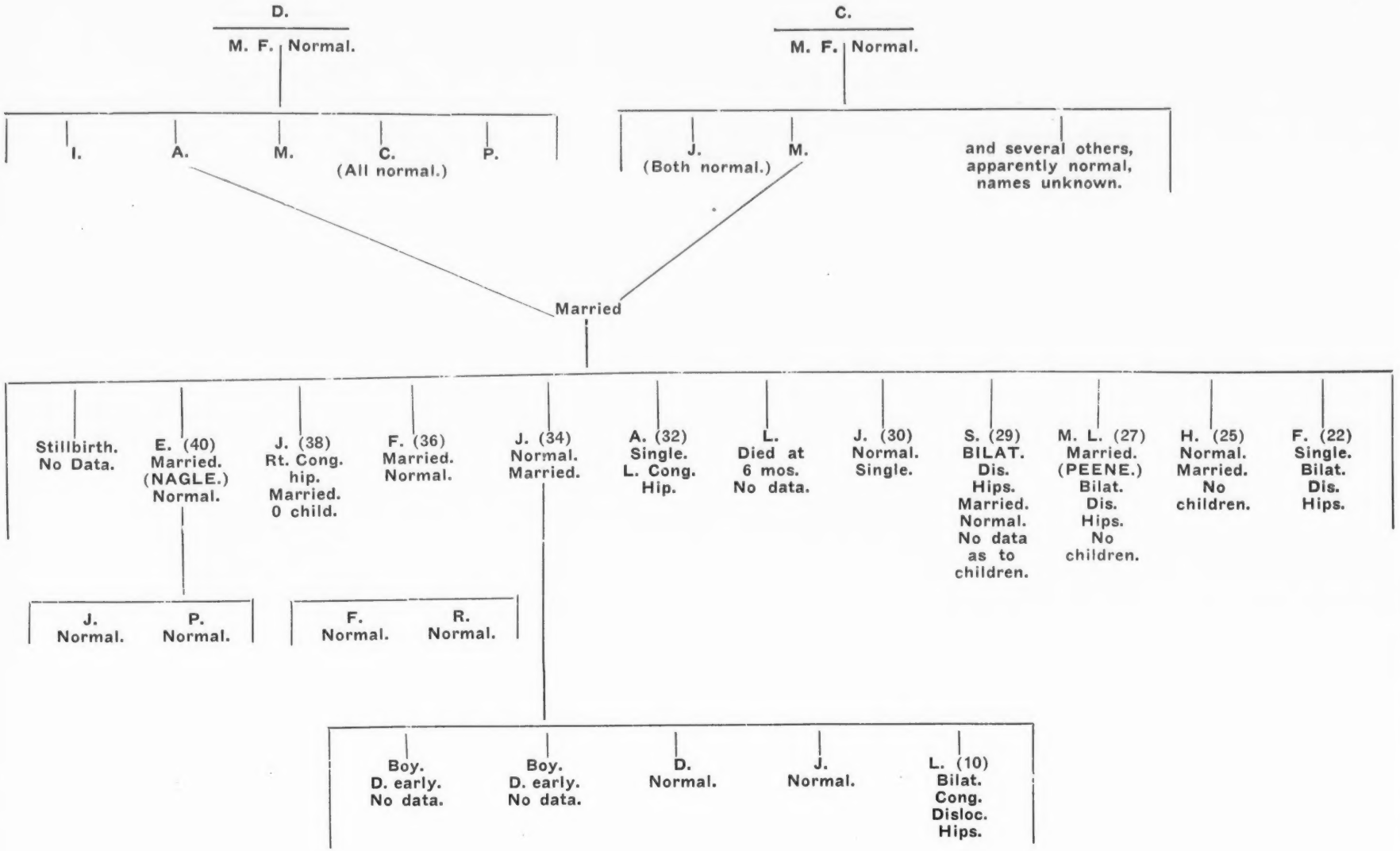
Vogel, in studying 200 cases, was of the opinion that in 30 per cent of these, heredity was an influence, even though remote in some instances. Putti, in reporting 1879 cases with a total of 2556 dislocations, was of the opinion that heredity played a part in an average of 13 per cent.

As to the nature of the atypical developmental condition which predisposes to this condition and which perhaps can be transmitted to subsequent generations, there is again uncertainty. McLean was of the opinion that the most probable mechanism was a deficit in the development of the cavity of the acetabulum as the three bones which constitute the ileum failed to fuse, a mechanism similar to that responsible for the production of cleft palate. Heusner was of the opinion that relaxation of the capsule was the important anatomical aberration. He also believed that the capsule of the female was more lax normally than that of the male, hence the greater incidence among females.

Others have insisted that trauma at birth was a factor. Trauma at birth is probably respon-

*From the Orthopedic Service of Dr. James W. Sever, Cambridge Hospital, Cambridge, Mass.

†Hanflig—Assistant Orthopaedic Surgeon to the Outpatient Department, Beth Israel Hospital. For record and address of author see "This Week's Issue," page 560.


D.
M. F. Normal.
I.
A.
M.
C.
(All normal.)
P.
C.
M. F. Normal.
J.
(Both normal.)
M.
and several others, apparently normal, names unknown.
Married
Stillbirth. No Data.
E. (40) Married. (NAGLE.) Normal.
J. Normal.
P. Normal.
J. (38) Rt. Cong. hip. Married. 0 child.
F. (36) Married. Normal.
F. Normal.
R. Normal.
J. (34) Normal. Married.
Boy. D. early. No data.
Boy. D. early. No data.
D. Normal.
J. Normal.
L. (10) Bilat. Cong. Disloc. Hips.
A. (32) Single. L. Cong. Hip.
L. Died at 6 mos. No data.
J. (30) Normal. Single.
S. (29) BILAT. Dis. Hips. Married. Normal. No data as to children.
M. L. (27) Married. (PEENE.) Bilat. Dis. Hips. No children.
H. (25) Normal. Married. No children.
F. (22) Single. Bilat. Dis. Hips.

sible for an occasional dislocation which ought to be considered a traumatic dislocation as distinguishable from the congenital variety.

The cases reported here, occurring as they do in two generations of one family, give further confirmation to the importance of heredity in the occurrence of congenitally dislocated hips.

As may be seen in the genealogical table, A. D. married M. C. So far as can be ascertained from the rather scanty data we have about these two families living in Ireland, none of them limped or presented any signs which might suggest abnormal hips. Beyond this generation we have no data whatsoever. They had 12 children.

The first was a stillborn male child, about whom we have no information whatsoever. The second was a female child named E. She is now 40 years of age, is married and has borne two children. She has perfectly normal hips and her children are normal. The third child, a boy J., is now 38 years old. He has a congenital dislocation of the right hip which has never been reduced. He has married and his wife has not borne any children. Next to follow was a male child, F. He is 36 years old and has perfectly normal hips. He has married and has two daughters both of whom show no evidence of dislocated hips.

J., now 34 years of age, was the next sibling. He has normal hips. He is married and his wife has borne five children. Of these, two boys died early in infancy. We have no information as to the condition of their hips. Two boys are living and well and have normal hips. Their only daughter who is now ten years old, has been treated since the age of 18 months for bilateral congenital dislocation of the hips.

A. was the next to be born. She is now 32 years of age and is single. She has an untreated congenital dislocation of her left hip. L. was the next child. He died at the age of six months of unknown cause, and we have no authentic information as to the condition of his hips. J., who is now 30 years old, was the next child. His hips are perfectly normal. He has not married.

S., who is now 29 years old, was the next child. She married a few years ago, traveled to the western part of the country and has not been heard of since. The other members of the family are certain that she was afflicted with bilaterally dislocated hips, and that she waddled in a manner similar to those of the family who were afflicted with the same disorder. They stated that such a diagnosis of her condition had been made by various surgeons. We do not know whether she has borne any children.

M. L., who is now 27 years of age, was the next child. Both hips are dislocated and she has never been treated for this condition. She has married recently but has not yet borne any children.

The last child was F., who is now 22 years of age. He also has bilateral dislocated hips. He has never been treated for these.

It is apparent, therefore, that of these 12 children, there are two concerning whose hips we have no data. Of the remaining ten, five had hips which were congenitally dislocated. In two of these it was a unilateral dislocation; in the remaining three it was bilateral. The only occurrence of this deformity in the second generation was in L., daughter of John, who has normal hips. None of the members of this family, who have congenitally dislocated hips, have borne children. It will be interesting to follow the future offspring in this group.

This series of cases is additional evidence for the importance of heredity in the production of this disorder.

REFERENCES

1 Heusner, L.: Ueber die angeborene Hüftluxation. Ztschr. f. orthop. Chir. 10:571, 1902.
2 McLean, A.: Congenital dislocation of the hip-joint.—Causes. Harper Hosp. Bull. 15:1 (June) 1904.
3 Putti, V.: Congenital dislocation of the hip. Surg. Gynec. Obst. 42:449 (April) 1926.
4 Vogel, K.: Zur Pathologie und Therapie der Luxatio coxae congenita. Deutsche Ztschr. f. Chir. 71:222, 1903-04.
5 Thompson, R.: The etiology of that form of dislocation of the hip-joint which is generally regarded as congenital. Lancet. 2:777 (Sept. 11) 1909.
6 Jahss, S. A.: Congenital dislocation of the hip in three generations. New York M. J. 108:550, 1918.

CLINICAL AND ECONOMIC FEATURES OF ARTHRITIS IN EX-MEMBERS OF THE MILITARY SERVICE*

BY PHILIP B. MATZ, M.D.†

THIS study of arthritis was conducted with the coöperation of several members of the American Committee for the Control of Rheumatism, notably Dr. Robert B. Osgood of Boston, Massachusetts, and Dr. Ralph Pemberton of Philadelphia, Pennsylvania. The purpose of the study was to determine the nature of the various types of joint disease, the probable predisposing and exciting etiological factors, the use of the various therapeutic regimens, and the results of treatment. In addition, data were obtained showing the amount of disability resulting from arthritis, the degree of the impairment of earning capacity, and the cost to the Government in the form of disability compensation, disability allowance, pensions and emergency officers' retirement pay because of joint disease.

In the conduct of the study, valuable assist-

*From the Research Subdivision, Medical and Hospital Service, Veterans' Administration.
Presented at the Conference on Rheumatic Diseases, held under the sponsorship of the American Committee for the Control of Rheumatism, New Orleans, May 9, 1932.
†Matz — Chief, Research Subdivision, Medical and Hospital Service, Veterans Administration, Washington, D. C. For record and address of author see "This Week's Issue," page 560.

ance was rendered by the medical officers who treated the patients and who subsequently furnished the data on a special form issued by the Medical and Hospital Service. The study included 450 patients hospitalized for arthritis and acute rheumatic fever. Of this number 448 were males and two were females. Four hundred and thirty-seven were white patients, nine were colored, and four belonged to the Indian race. Four hundred and fourteen, or 92 per cent, of the total number were born in the United States, and 36, or eight per cent, were born in foreign countries. Four hundred and five were World War veterans; 28 were veterans of the Spanish-American War; ten were veterans of other wars or expeditions; and seven were veterans of two or more wars.

CLASSIFICATION OF JOINT DISEASE

The classification of the joint diseases for which the patients were hospitalized was, in the main, in accordance with suggestions made by various members of the American Committee for the Control of Rheumatism. For the purpose of this study it was finally decided that the joint diseases should be classified according to the following nomenclature which carries with it well-defined criteria for diagnosis:

Atrophic Arthritis

Criteria for diagnosis:

1. Mode of onset may be gradual but is sometimes acute with a febrile attack. Earlier age incidence, birth to 45 years of age.
2. Bilateral symmetry: usually more or less laterally symmetrical.
3. Initial changes: periarticular and articular swelling, often free fluid, proliferation of synovial membrane.
4. Movement: considerable limitation.
5. Atrophy of muscles begins early and increases to wasting if disease is unchecked.
6. Joints usually first affected: midphalangeal and metacarpophalangeal joints of hands.
7. Appearance of swelling of joints: fusiform.
8. Late changes: deformities and contractures, subluxations, fibrous or bony ankylosis.
9. Radiographs:
   (a) Early: no bony or cartilaginous changes of articular ends. Slight diminished density of bone shadow. Increased density of articular soft parts.
   (b) Late: marked diminished density of bone shadow. Loss of bone substance or articular ends, subluxation, ankylosis.

Hypertrophic Arthritis

Criteria for diagnosis:

1. Usual mode of onset: insidious, afebrile, later age incidence, 45 years or older.
2. Bilateral symmetry: often symptomatically monarticular, asymmetrical.
3. Initial changes: endarticular. Slight ridging and tenderness at articular margins.
4. Movement: (Early), little interference. (Late), limitation, slight permanent flexion. If joint "mice", lockings.
5. Atrophy of muscles: only late as a result of non-use.
6. Joints first affected: larger joints and terminal joints of fingers, "Heberden's nodes." Symptoms most commonly first felt in one knee.
7. Appearance of swelling of joints: irregular rather hard swelling. Gnarled appearance.
8. Ankylosis—rare.
9. Radiographs:
   (a) Early: delicate spicules of calcium to be seen at articular margins. No diminished density of bone shadow, no increased density of articular soft parts.
   (b) Late: chondro-osseous ridging of articular margins, hyperostoses. Irregular notched articular surfaces, no subluxation, no true bony ankylosis except in spine where impinging spicules may coalesce.

Arthritis Due to Specific Agents

Criteria for diagnosis:

1. Characteristics often identical with atrophic arthritis except for supposed or certain "infectious" origin, and the actual proved presence of specific bacteria in the joint fluid or tissues.
2. The type of arthritis should be indicated according to the etiological classification below:
   (a) Tuberculous
   (b) Gonorrheal
   (c) Pneumococcic
   (d) Typhoid
   (e) Syphilitic
   (f) Staphylococcic
   (g) Other types (specify)

Rheumatic Fever

Criteria for diagnosis:

1. Acute attacks of migratory arthritis, recurring on an average of two to three times, and rarely resulting in chronic arthritis; when the latter does occur, it is usually of the atrophic type. In some instances, it results in cardiac injury after the first or subsequent attacks.

Gout

Criteria for diagnosis:

1. Usual mode of onset: acute febrile.
2. Usual age of onset: 35 to 50 years.
3. Bilateral symmetry: usually asymmetrical.
4. Initial changes: the first confined to articular cartilages.
5. Movement: little limitation after recovery from acute attack in early stage.
6. Wasting of limbs—only in late stages.
7. Joints first affected: almost always metatarsophalangeal articulation,—great toe affected first.
8. Appearance of swelling of joints: irregular.
9. Ankylosis: rare.
10. X-ray findings: somewhat resembles hypertrophic arthritis with deposits of sodium urate.
11. Blood uric acid increased at time of typical attack (5 mgm. or more per 100 cc. blood).
12. Tophi usually present.

Atrophic Arthritis of Spine and Pelvic Joints

Criteria for diagnosis:

1. Same general characteristics of type as in extremity joints, except for frequent calcification of vertebral ligaments, especially the anterior common ligament.

2. Early limitation of spinal motion.
3. Early limitation of chest expansion and involvement of costovertebral articulations.
4. Rarely referred pain to peripheral nerves.
5. Marked tendency to ankylosis and kyphotic deformity.
6. Bony fusion of sacro-iliac joints common.
7. Disease often called "Poker Back," "Marie-Strümpell" type, spondylitis deformans, or spondylose rhizomelique.

HYPERTROPHIC ARTHRITIS OF SPINE AND PELVIC JOINTS

Criteria for diagnosis:

1. Same general characteristics of type as in extremity joints except for rather early limitation of spinal motion.
2. Chest expansion and costovertebral articulations not usually affected.
3. Common referred pain, e.g., "intercostal neuralgia" and "sciatica".
4. When spurs on bodies of vertebrae impinge, localized ankylosis may occur.
5. Disease often called "osteoarthritis of the spine."

Of the 450 cases of arthritis hospitalized and included in this study 213, or 47.4 per cent, were classified as hypertrophic arthritis; 172, or 38.2 per cent, were atrophic arthritis; 31, or 6.9 per cent, were hypertrophic arthritis of the spine and pelvic joints; 14, or 3.1 per cent, were arthritis due to specific agents; ten of these were gonorrheal, two were tuberculous, and two of the arthritides were syphilitic; ten, or 2.2 per cent, were classified as rheumatic fever; five, or 1.1 per cent, were classified as atrophic arthritis of the spine and pelvic joints; and five cases, or 1.1 per cent, were classified as combined hypertrophic and atrophic arthritis.

TYPE AND SITE OF JOINT DISEASE

Pemberton[1] states that in all cases of arthritis the knee is the site of most frequent involvement. In a study of a group of soldiers hospitalized for arthritis during the World War he found that the principal sites, in the order of frequency, were as follows: knee 62 per cent; ankle 35.1 per cent; hip 33.7 per cent; and shoulder 31.7 per cent. In a group of male civilian arthritics Pemberton found the principal sites, in the order of frequency, were knee 65 per cent; hand 46.9 per cent; shoulder 42 per cent; ankle 40.9 per cent; foot 40.9 per cent; and wrist 32.7 per cent.

The 213 patients with hypertrophic arthritis gave evidence of the involvement of 599 joints, or an average of 2.8 joints per patient. The principal sites affected in the order of frequency, were spine, knee, shoulder, hip, ankle, elbow, sacroiliac joint, wrist, hand, foot, heel, and sternoclavicular joint.

One hundred and seventy-two patients were under treatment for atrophic arthritis. Among these there was a history of the involvement of 643 joints, or an average of 3.7 joints per patient. The principal sites affected, in the order of frequency, were knee, ankle, shoulder, hip, wrist, spine, elbow, hand, foot, heel, and sacroiliac joint.

Five patients were under hospitalization for a combined hypertrophic and atrophic arthritis with involvement of 23 joints, or an average of 4.6 joints per patient. The joints affected, in the order of frequency, were knee, shoulder, ankle, spine, hip, sacroiliac joint, elbow, wrist and hand.

Thirty-one patients were under hospitalization for hypertrophic arthritis of the spine and pelvic joints. A total of 66 joints were affected, or 2.1 joints per patient.

Five patients were under treatment for atrophic arthritis of the spine and pelvic joints, with a total of 11 joints affected, or an average of 2.2 joints per patient. Fourteen patients were under treatment for arthritis due to specific agents with a total of 32 affected joints, or 2.3 joints per patient. The joints involved, in the order of frequency were knee, shoulder, ankle, hip, spine, heel, hand, foot, and wrist. Ten patients were under treatment for rheumatic fever with involvement of 43 joints, or an average of 4.3 joints per patient. The sites affected, in the order of frequency, were ankle, knee, hand, wrist, shoulder, foot, elbow, hip, and spine. Of the total of 450 patients, the data showed that 1417 joints were involved, or an average of 3.1 joints per patient. The principal sites of involvement in the order of frequency were knee, spine, shoulder, ankle, hip, wrist, elbow, sacroiliac joint, hand, foot and heel.

MOST FREQUENT COMBINATIONS OF AFFECTED JOINTS CORRELATED WITH TYPE OF ARTHRITIS

A study was made to ascertain the most frequent combinations of affected joints in the case of hypertrophic and atrophic types of arthritis.

In 75 cases of hypertrophic arthritis, the spine was the most frequent site of the disease where but one joint was affected. As the arthritic process spread and more joints became involved, the following combinations of sites were noted, the spine and shoulder; the spine, shoulder, and elbow; the spine, shoulder, elbow, and knee; the spine, shoulder, hip, knee, and ankle. In patients with involvement of six or more joints, the spine, shoulder, hip, knee, ankle, wrist, and elbow were the most frequent sites.

In 26 cases of atrophic arthritis, the knee was the most frequent site of the disease where but one joint was affected. As the disease process spread to other sites, the following combinations of joints were most frequently noted: the knee and ankle; the knee, ankle, and hip; the knee, ankle, hip, and shoulder; the knee, ankle, shoulder, wrist, and hand. In patients with involvement of six or more joints, the knee, ankle, shoulder, wrist, hand, foot, elbow, hip, and spine were the most frequent sites of the arthritic process.

HEREDITARY OR FAMILIAL HISTORY

Cecil[2] maintains that heredity plays an important part in the etiology of arthritis. Nearly

every patient with Heberden's nodes will give a history of a mother or father who was afflicted with the same condition. Swaim[3] states that atrophic arthritis has a distinct hereditary tendency. Pemberton[1] in collaboration with E. G. Peirce in a study of a group of 1100 cases of chronic arthritis, showed that hereditary influences, either direct or collateral, were seen in 58 per cent of the cases. These observers state that this does not necessarily represent direct transmission from parent to child of the tendency to develop arthritis, but rather a general familial background on which the disease may develop. This is borne out by the frequency with which uncles or aunts and brothers or sisters have been affected with this disease.

In the British Ministry of Health inquiry Glover[4] found that heredity played the following rôle in the etiology of arthritis: of the group of male patients with atrophic arthritis, there was an hereditary history in 36 per cent of the cases; in the group of cases with hypertrophic arthritis there was an hereditary history in 32 per cent; and in patients affected with gout, heredity played an etiologic part in 20 per cent of the group.

Fisher[5] is of the opinion that there is an inherited predisposition to arthritic affections. He states further that this predisposition may be acquired, as evidenced by the frequent antecedent history of illness, exposure, nervous strain or definite injury to the affected joint. Coburn[6] maintains that observations of the "rheumatic family" suggest that there is possibly a tendency to the development of the rheumatic state among blood relations not living together, and furthermore, that this tendency may be hereditary. The general opinion prevails that the strongest hereditary predisposition to arthritis is seen in gout; next in atrophic arthritis; and lastly in cases of hypertrophic arthritis. In contradistinction to what has been said, there are some observers, notably A. E. Garrod, who hold that heredity plays no part in the inception of arthritis.

In this study but 79, or 17.6 per cent, of the group of patients with joint disease gave a positive hereditary, familial, or a combined hereditary and familial history of the disease. The term "hereditary" refers to the presence of the disease in a parent, grandparent, uncle, or aunt; the term "familial" refers to the presence of the disease in a sister, brother, or in a cousin.

Of the 79 cases, 54, or 68.4 per cent, gave an hereditary history; 18, or 22.8 per cent, gave a familial history; and seven, or 8.8 per cent, gave a combined hereditary and familial history of joint disease.

Fifteen and five-tenths per cent of the group with hypertrophic arthritis gave an hereditary, familial or a combined hereditary and familial history of joint disease; 21.5 per cent of the group with atrophic arthritis gave an hereditary, familial, or a combined hereditary and familial history; 21.4 per cent of the group with arthritis due to specific agents gave an hereditary history; and of the small group hospitalized for rheumatic fever there was no hereditary or familial history of the disease.

In those cases in which there was an hereditary history of arthritis, the father was the member of the family most frequently affected and the mother was affected next in frequency. In those cases with a familial history, the sister was the member of the family most frequently affected, and the brother was next in frequency. In those cases in which there was a combined familial and hereditary history of arthritis, the mother and sister, and the mother, father, brother and two sisters were the members of the family most frequently affected.

PREDISPOSING FACTORS

Pemberton[1] maintains that arthritis may follow attacks of ill health of many kinds, even periods of fatigue, worry, physical strain or exposure; in other words, any factor which interferes with general health may predispose to the disease. This observer maintains that one of several predisposing causes of arthritis is an abnormal colon. By this is meant that arthritis may develop because of an abnormal physiological function together with increased putrefaction and fermentation due to bacterial activity in a colon of greater caliber, greater length, and of a more convoluted appearance than normal.

Millard Smith[7] in a study of a group of 102 patients with atrophic arthritis, found 52, or 50 per cent, gave a history of depleting and unbalancing experiences to which the joint disease might be attributed. Such experiences may have a profound emotional or physical predisposing effect and may lead to the inception of arthritis.

Cecil[2] maintains that the increased susceptibility to arthritis is probably due to a combination of improper diet and exposure to cold. He further states that, in hypertrophic arthritis, overweight and advancing years are the two important predisposing factors.

Swaim[3] is of the opinion that it is unknown just which one of many apparent causes precipitates the final break in compensation leading to arthritis, but such factors as exhaustion, chilling, infection, pregnancy, nervous shock, or postural defects may become causes in individual instances.

Glover[4] is of the opinion that the etiology of chronic arthritis is still imperfectly understood. It is probable that there are several important predisposing factors leading to its production, in addition to the exciting causes, such as faulty metabolism, trauma, occupational stress, mental stress, and derangement of endocrine balance.

In this study 266 of the total number of 450 patients with arthritis gave a history of one or

more predisposing factors. Altogether, there were 608, or an average of 2.3, predisposing causes among the 266 patients. The most frequent factor was undue exposure to prolonged chilling; next in frequency was undue exposure to dampness. The next most frequent predisposing factors were severe physical or mental fatigue, trauma of joint, severe mental or nervous shock, and overuse of joint. The study disclosed the fact that both hypertrophic and atrophic arthritis had similar predisposing factors. It is of interest to note that trauma was a possible predisposing factor in 78, or 29.3 per cent, of the group of 266 patients and that it was reported as having played a possible rôle in the causation not only of cases of hypertrophic arthritis but in other types of joint disease as well. In some of these cases the part played by trauma as a possible predisposing factor may be explained on the basis of a diminished resistance of the tissues in and around the joint which may have resulted in the inception of arthritis.

BODY BUILD

Pemberton[1] holds that the body build which seems most frequently associated with the tendency to arthritis is that of the slender, long-bodied, possibly enteroptotic individual. This observer further states that there is no implication that other types of physique may not show a similar tendency, but it seems to be most marked in connection with the kind of individual mentioned, especially as regards the susceptibility to atrophic arthritis. Swaim[3] states that atrophic arthritis appears in the slender, light-boned woman, the congenital visceroptotic type. It is almost never found in heavy-boned individuals. Smith[8] in a study of a group of patients with atrophic arthritis found that the asthenic type of individual was frequently susceptible to this form of arthritis.

In the group studied there was a suggestion of an increased susceptibility to atrophic arthritis among slender, long-bodied and enteroptotic subjects. Thus of 172 cases of atrophic arthritis, 52.9 per cent were of this type as compared with 40.1 per cent among subjects of stocky build; seven per cent were of other types of physique.

AGE AT TIME OF ONSET OF ARTHRITIS

Pemberton[1] in a study of a group of male arthritics found that the greatest incidence of involvement was between 36 and 40 years of age. However, there was a rather unexpectedly high incidence in the group between 16 and 20 years of age. Glover[4] maintains that atrophic arthritis most frequently begins between 25 and 40 years, while hypertrophic arthritis has its inception usually between 40 and 55 years of age. Garrod states that, in his experience, arthritis is most common between 40 and 50 years of age. Coburn[6] is of the opinion that age is among those influences which are made use of by nature in the maturation of the rheumatic process. Smith[8] holds that atrophic arthritis is commonly seen in individuals between 20 and 30 years of age.

Of the group of 450 arthritics included in this study, 116, or 25.8 per cent, gave evidence of joint disease within the age group 30-35; 113, or 25.1 per cent, incurred the arthritic condition within the age group 25-30; 97, or 21.6 per cent, incurred arthritis within the age group 20-25; and 55, or 12.2 per cent, incurred arthritis within the age group 35-40. The remaining cases were distributed in various age groups below 20 years and above 40 years but there were no distinctive age groups other than those mentioned. In this connection it was noted that a number of the cases of hypertrophic arthritis had their inception in the younger age groups. It is realized that, according to the modern concept, hypertrophic arthritis usually occurs between 40 and 45 years of age or later. In the opinion of the writer there is a question whether one can afford to be dogmatic in such a concept. Cases of hypertrophic arthritis give a history of an insidious onset with little or no subjective symptomatology or signs of joint disease, in other words, it is difficult to establish the exact time of onset of this type of arthritis. As a matter of fact the etiology of hypertrophic arthritis is not definitely known and the mode of its onset is not clear, so that to maintain that this type of joint disease does not occur before a certain age is too arbitrary a stand. It is possible that many of the cases of hypertrophic arthritis reported in this study in which the onset was in the earlier age groups began as an atrophic form of arthritis, upon which hypertrophic changes subsequently became superimposed and, at the time of the study, the clinical symptoms and signs, as well as the x-ray findings, were those of the latter type of joint disease.

Further study indicated that the mean age of onset of the 213 cases of hypertrophic arthritis was 31 years; among 172 cases of atrophic arthritis the mean age of onset was 28.9 years; in five cases of combined hypertrophic and atrophic arthritis, the mean age of onset was 27 years; in 31 cases of hypertrophic arthritis of the spine and pelvic joints the mean age of inception was 30.6 years; in five cases of atrophic arthritis of the spine and pelvic joints the mean age of inception was 25.6 years; in 14 cases of arthritis due to specific agents the mean age of onset was 35.1 years; and in 10 cases of rheumatic fever the mean age of onset was 35.8 years. Considering the whole group of 450 arthritics, the oldest patient was 64 years of age at the

time of onset, the youngest 12, and the mean age of the whole group at the time of onset of arthritis was 30.3 years. It was further noted that of the group studied no case of arthritis of the spine, arthritis due to specific agents, or rheumatic fever had its inception before 20 years of age.

WEIGHT AT TIME OF INCEPTION OF ARTHRITIS

Much has been written on the nutritional state of the arthritic prior to the inception of the joint disease. In order to obtain information on this point the weight of a group of 378 patients was correlated with the age and height at the time of the inception of the joint affection to determine whether it was within normal range (+5 to —5 per cent). If above or below the normal range an estimate was made of the per cent of increase or decrease of weight as compared with normal. In this group of 378 patients with arthritis, 48.2 per cent were above the standard weight at the time of the onset of arthritis; 21.4 per cent were below the standard weight; and 30.4 per cent were within the normal zone. It is of interest to note that of 182 arthritics above the standard weight at the time of onset of arthritis, the largest group, 72, showed a deviation of 11 to 20 per cent from the standard weight; the next largest group, 58 in number, showed an increase over the normal weight of six to ten per cent. Of 81 cases below the standard weight at the time of onset of arthritis, the largest number, consisting of 42 cases, showed a deviation from normal of six to ten per cent; and the next largest number, 35 cases, showed a deviation from the normal weight of 11 to 20 per cent.

Further study of the group of 378 cases indicated that 169 patients gave evidence of hypertrophic arthritis, of which number 45 per cent were above the standard weight; 22.5 per cent were below the standard weight for their age and height. One hundred and fifty-four patients gave evidence of atrophic arthritis, of which number 50.6 per cent were above the standard weight, and 19.5 per cent were below the standard weight. Twenty-seven cases gave evidence of hypertrophic arthritis of the spine and pelvic joints, of which number 51.9 per cent were above the standard weight, and 18.5 per cent were below the standard weight. It is therefore seen that the largest group of patients who developed arthritis gave evidence of overweight at the time of the inception of joint disease, and the next largest number were within normal weight for their height and age. Twenty-one and four-tenths per cent of the group of 378 patients were below the standard weight at the time of the inception of the joint disease.

INFLUENCE OF DIET UPON INCEPTION OF ARTHRITIS

It has been the experience of a number of observers that a reduction of the caloric intake by arthritics results in an improvement of the joint disease, particularly if carbohydrates are reduced.

Pemberton[1] has recommended the use of a restricted dietary, particularly of the carbohydrate portion, in the treatment of arthritis. Fletcher[9] has noted the value of carbohydrate reduction plus vitamin increase in the treatment of joint disease. Some of the factors which may cause arthritis are an overindulgence of food, particularly carbohydrates; reduced vitamin and protein intake; or an imbalance of the various components of the diet. These factors may result in a lowered resistance of the individual, a spread of a focal infection to one or more joints and the inception of arthritis. Of the total number of arthritics studied 88, or 19.6 per cent, gave a history of overeating, while in 45, or ten per cent, there was a history of undereating. Eleven and three-tenths per cent of the group gave a history of the ingestion of a predominant diet of carbohydrates prior to the onset of arthritis; 32.2 per cent ingested an excessive amount of protein; 1.3 per cent partook of an excessive amount of fat; and 5.3 per cent of the patients gave a history of the ingestion of excessive amounts of various food stuffs in combination. Of the total number, 49.8 per cent of the patients gave a history of the ingestion of a normal diet.

One cannot draw any definite conclusions from the data just cited inasmuch as they are based upon information supplied by the patients themselves, and are not sufficiently accurate to indicate that there was an ingestion of an excessive amount of a certain foodstuff, or that an overindulgence of food may have acted as a predisposing cause of the arthritic process.

It is conceivable that a diet in which there is an imbalance of certain of the components, including the mineral and vitamin contents, with a disturbance of the normal ratio of the various foodstuffs, may lead to the inception of joint disease.

CHRONIC CONSTIPATION

The relationship of chronic constipation to arthritis is not thoroughly understood. Opinion prevails that it acts in a manner similar to a focal infection. If the constipation is due to a functional disease of the intestine such as spastic colitis, with a delayed movement of the bowel contents, there is an absorption of toxins which may be carried to a joint and produce arthritis. Another mode of action of the intestinal contents is the aggravation or excitation of a focal infection elsewhere in the body which, in turn, may lead to the inception of arthritis.

Pemberton[10] describes abnormal conditions of the intestinal tract which he found present in the course of chronic arthritis and which

often preceded the joint disease. These abnormalities were observed in the colon and consisted of elongation, widening, tortuosity with resulting inertia of the colon. Fletcher[9] showed that following proper lines of therapy the bowel returned to normal, and clinical betterment of the patient ensued. The treatment consisted of colonic irrigation as well as a restricted carbohydrate regimen, an increased vitamin intake, and the ingestion of an adequate amount of proteins. Smith[11] in a study of a group of 102 atrophic arthritics, found that chronic constipation was present in 30 per cent of the cases. Of the group of 450 patients studied but 13.8 per cent gave a history of marked constipation prior to the onset of the arthritic condition. These data do not confirm the findings and opinions of other observers that constipation and intestinal stasis are etiological factors of arthritis.

ENDOCRINE DISTURBANCE

Fisher[5] holds that it is probable that disordered endocrine function plays an important part in the inception of many of the more chronic forms of arthritis, especially primary hypertrophic arthritis occurring after middle life, the type noted in the knees of women, the onset of which corresponds with the menopause. A similar form of arthritis occurs in men with involvement of the hip or spine.

The principal pathological finding is a degeneration of the articular cartilage. It is present in persons of advanced years and is probably one of a number of senile manifestations which may be attributed to dysfunction of certain of the internal secretory glands leading to an impoverishment of the blood supply to the joints.

Pemberton[1] states it seems probable that the influence of the endocrine system exerts itself chiefly in connection with those changes which may be characterized as senile, and that these, rather than any gland or glands, per se, afford the background from which the disease springs, particularly the degenerative type of arthritis. Llewellyn refers to the prodromata and symptoms of atrophic arthritis as due partly to hypothyroidism. H. K. Thompson is of the opinion that atrophic arthritis is associated with hyperthyroidism while hypertrophic arthritis may be an accompaniment of hypothyroidism.

Glover[4] states that the boundaries between the metabolic and endocrine groups of joint disease, and between these and the infective group, are indefinite. In those cases in which a metabolic disturbance appears as the primary cause, it might be secondary to toxins of an undiscovered focal infection. Faulty endocrine balance is often known to be caused by toxins emanating from a focal infection which is not clinically discernible.

Of the total number of 450 cases but eight, or 1.8 per cent, gave a history of some endocrine disturbance; four of the group were associated with hyperthyroidism; two with gonadal hypoactivity; and two cases with pituitary hypoactivity.

From the above it would appear that there is no relationship between endocrine disturbance and the inception of arthritis in the group studied.

HISTORY OF ALLERGIC MANIFESTATIONS

Smith[11] in a study of a group of patients with atrophic arthritis, from the standpoint of allergy, found that an abnormal reactibility was common to a significant number of the patients. However, the data were incomplete and the findings were not conclusive. It has been suggested that atrophic arthritis is a form of bacterial allergy, that is, a hypersensitive joint reacting in an anaphylactic manner to toxins coming from some distant focus of infection.

Zinsser maintains that acute rheumatic fever represents an allergic state, because, in anaphylaxis, joint symptoms may occur which are similar to those seen in arthritis. Also in acute arthritis culture of the joint fluid usually shows it to be sterile.

Pemberton[1] states that it is conceivable that when the body has long harbored a definite infection it may become allergic to substances given off from the growing organisms. This concept, however, is not clear and conclusions drawn from such an hypothesis are not warranted.

Of the total of 450 patients, 24, or 5.3 per cent, gave a history of some allergic manifestation or skin disease. Eleven of the patients were affected with hypertrophic arthritis; ten had atrophic arthritis; one had a combined hypertrophic and atrophic arthritis; and two patients were affected with hypertrophic arthritis of the spine and pelvic joints. Of the 24 allergic arthritics, ten gave a history of dermatitis; six bronchial asthma; three urticaria; three psoriasis; and two gave a history of hay fever.

From the above it would appear that in this group of arthritis allergic manifestations were not of sufficient prominence to justify the conclusion that they played any part in the causation of the joint disease.

RELATION OF GEOGRAPHICAL ENVIRONMENT TO INCEPTION OF ARTHRITIS

Coburn[6] refers to a group of patients in New York City with rheumatic disease whose rheumatic activity subsided while in the tropics, but there was a definite recrudescence of the disease shortly after their return to New York during the hot summer months. This writer has observed that the rheumatic state is prevalent and severe in North America between latitudes 50 and 40 degrees North, and it is not uncommon between 40 and 30 degrees North. On the other hand it is rare between 30 and 20 degrees

North, and is almost unknown between the tropics of Cancer and Capricorn. Furthermore, Coburn maintains that the rheumatic state is rare between 20 and 30 degrees South, and is common between 30 and 40 degrees South.

Glover[4] states the opinion prevails that atrophic arthritis is more prevalent in Ireland than in England and that the people in northern European countries are more commonly affected with chronic arthritis than those of southern European countries. Chronic arthritis, according to Glover, appears to be almost as common in the Eastern States of the United States as in England.

An attempt was made to classify the States and countries of residence of a group of 185 arthritics at the time of the onset of the joint disease. It was found that the largest number, 57, or 30.9 per cent, gave a history of the inception of arthritis while in France. The next largest number, 52, or 28.1 per cent, showed evidence of the onset of arthritis in certain of the States of the North Central Group. The latitude of this group of States has a range between 35 and 49 degrees North. Twenty-eight, or 15.1 per cent, of the group gave a history of the inception of arthritis while residing in certain of the plateau States, the latitude of which has a range between 31 and 49 degrees North. The principal individual countries or States of residence at the time of the onset of arthritis, together with the number developing the joint disease, in the order of frequency were France 57 cases; Montana 21; Michigan ten; Illinois eight; Missouri seven; New York six; Indiana five; and Wyoming five cases.

THE RÔLE OF OCCUPATION IN THE ETIOLOGY OF ARTHRITIS

There are a number of occupations which by their very nature may be conducive to arthritis, either of the atrophic or the hypertrophic type. For instance, it is conceivable that such occupations as butchering, which requires frequent visits to the refrigerator, farming or ranching, which are associated with outdoor work, and work entailing the constant use of certain joints, such as mining, blacksmithing, tailoring, typing, etc., may be causative factors of arthritis.

Fisher[5] refers to occupational joint affections as compensatory conditions. By this he means that the joint adapts itself to the mechanical irritation by the production of pathological changes characteristic of arthritis. A review of the occupational data showed that of the 450 arthritics, included in this study, 128 were farmers and ranchers by occupation; 36 were mechanics; 31 were laborers; and 19 were miners. Altogether 214, or 47.5 per cent of the group, gave a history of having been engaged in occupations which are accompanied by exposure or mechanical traumatisms and which may have acted as predisposing factors in the causation of arthritis.

A complete list of references will appear at the end of this article, which is to be continued.

THE CHANCES OF DYING FROM DIPHTHERIA

Among the outstanding triumphs of preventive medicine in the twentieth century is the control gained over diphtheria. With the single exception of typhoid fever, there has been a greater per cent reduction in the death rate from diphtheria, since the beginning of the century, than from any other disease. The signal success that has been scored in this field is reflected in the great diminution that has taken place in the risk, as measured by the chances per thousand, of dying from this disease.

Diphtheria, being almost exclusively a childhood disease, the risk of eventually dying from this cause falls to a very low figure at adult ages. But at birth, in the year 1920, the chances of eventually falling a prey to this disease were 7.1 per thousand for white males and 6.7 per thousand for white females. In 1925, the corresponding chances were reduced by almost 50 per cent, namely, to 3.9 and 3.7, respectively. In our last census year, 1930, these figures had fallen to 2.4 and 2.3, practically one-third of the figure for 1920. We have here a reduction by 66 per cent of the initial value, in the brief course of a decade. Today, the probabilities are undoubtedly lower, although the computations have not as yet been made.

While, from the standpoint of importance as a cause of death, the interest in diphtheria is concentrated almost wholly at the younger ages, an inspection of the figures at adult ages brings out a feature of singular interest. It will be noted that, small as are the probabilities of dying from this disease at ages fifteen and over, they are consistently higher or, in no case lower for white females than for white males. This is a somewhat mournful testimony to the devotion of the female sex to the welfare of the young of the race. For it seems probable that the excess of mortality from diphtheria among adult females, as compared with males of the same age, is due to infection caught by mothers, elder sisters, and nurses, in caring for young children attacked by the disease. It will be noted, that among the younger children themselves, the probability of dying from diphtheria is higher for boys than for girls, so that there is no reason to assume any inherent bias of the female sex toward death from this course, as compared with males.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

EDITED BY RICHARD C. CABOT, M.D.
F. M. PAINTER, A.B., ASSISTANT EDITOR

CASE 19371

AORTIC VALVE DISEASE OF QUESTIONABLE ETIOLOGY

MEDICAL DEPARTMENT

PRESENTATION OF CASE

DR. RICHARD B. CAPPS:* *First admission.* This is the case of a forty year old white single chauffeur who entered the hospital complaining of dyspnea of four months' duration.

At his first admission, five years before the second, he gave a history of an attack of acute dyspnea and orthopnea five years previously. The attack lasted five or six days and required bed rest. He recovered from that and was perfectly well and able to continue his work, which was not unusually hard, until five weeks before admission. At that time he caught cold, developed dyspnea on exertion and had a sense of oppression under the sternum on exertion. He also developed attacks of nocturnal dyspnea and was quite orthopneic. He was put to bed for a few days and given digitalis, then returned to work. He was fairly well until three weeks before admission, when he was in an automobile accident. Following that he had a severe attack of dyspnea and thought he was going to die. He was pulled out of that attack by his doctor and remained in bed, getting up at the end of a week. A week before admission he developed sharp pain in his left chest on breathing.

The past history showed that he had had during childhood some indefinite joint symptoms. At the age of twenty-five he had had inflammatory rheumatism involving a number of the larger joints; we could not find out any more about it than that. He had had a penile sore at the age of twenty. He had been married twice and had no children.

Examination showed a poorly nourished and developed man in slight respiratory distress, slightly cyanotic. There were moist râles at both lung bases. The left chest was prominent in the precordial region. The heart beat was heaving and shook the whole body. The apex impulse was seen and felt in the anterior axillary line. At the base there was a to and fro murmur, loudest at the aortic area, with a systolic thrill. The aortic second sound was less than the pulmonic second, and what was heard may have been transmission from the pulmonic second. At the apex there was a diastolic thrill, a to and fro murmur and also a mid-diastolic rumble. The pulse was forceful and of the collapsing type. There was a pistol shot over the brachials, which were moderately sclerosed. The blood pressure was 142/60. There was an old penile scar. The ankle jerks were absent. The left knee jerk was absent, the right very weak.

Two Hinton blood tests were strongly positive, one Wassermann moderately positive, one negative. A lumbar puncture showed a first zone type of colloidal gold starting with fours, 46 cells, all lymphocytes, and a strongly positive Wassermann. An electrocardiogram showed slight right axis deviation.

X-ray examination showed general enlargement of the heart and probable dilatation of the ascending aorta consistent with rheumatic heart disease.

Digitalis was given, potassium iodide and mercury. Twelve days after admission the patient was discharged.

History of interval. He went home and was followed in the Outpatient Department. He was given a number of courses of tryparsamid and continued on digitalis. He was fairly well, with only moderate dyspnea on exertion, until five weeks before admission ten months later. At that time he had nocturnal dyspnea again. Three weeks before readmission he became orthopneic and noticed marked increase in edema, which was present in the morning as well as at night. For one day before readmission he had nausea and vomiting and felt extremely weak.

Second admission, ten months after his previous discharge. Physical examination was essentially the same as before except for a blood pressure of 124/30 and probable fluid at both bases. There was marked edema. He was very weak and died after being in the ward for two days.

CLINICAL DISCUSSION

DR. CAPPS: At his first admission it was thought that he had rheumatic heart disease with central nervous system syphilis. The diagnosis at his first discharge was rheumatic and syphilitic heart disease with aortic regurgitation and syphilis of the central nervous system. Dr. Paul White felt that he probably had a superimposed luetic aortitis, but could not prove it.

The diagnosis at his second discharge was the same as that at his first plus questionable mitral stenosis and regurgitation and congestive heart failure.

DR. TRACY B. MALLORY: Dr. Means, do you remember this man at all? The case was some time back.

DR. J. H. MEANS: I do not remember him. I

*Recently senior interne on the East Medical service.

made the following note in the record: "There is no doubt that anatomically the chief lesion is aortic regurgitation and left ventricular hypertrophy. X-ray shows some right sided enlargement also. The problem is etiology. He has a story of chancre and has stiff pupils and no knee jerks, therefore in all probability has tertiary syphilis. In spite of this we believe the heart lesion more probably rheumatic, chiefly because of the story of early dyspnea dating back into childhood and of the bulging over his heart, which suggests a long-standing process. There is a systolic too at the base, and Dr. Graybiel feels a thrill. This suggests some element of stenosis, which also favors the rheumatic theory."

I should like to ask Dr. Sprague about the right axis deviation. Apparently the patient had a huge left ventricle. One wonders why the cardiographic finding was what it was.

DR. HOWARD B. SPRAGUE: I think in those cases in which we have had this difficulty with luetic and rheumatic etiology, when we have had right axis deviation we have found rheumatic heart disease. I do not know what his right ventricle shows. Whether it is a matter of overbalancing the left ventricle we do not know.

DR. MEANS: You mean that the left ventricle was huge but the right one was more huge, so to speak.

CLINICAL DIAGNOSES (FROM HOSPITAL RECORD)

Rheumatic heart disease with aortic regurgitation and stenosis and questionable mitral stenosis and regurgitation.
Tertiary syphilis probably with syphilitic heart disease and aortitis; taboparesis.
Congestive heart failure.

ANATOMIC DIAGNOSES

Rheumatic heart disease.
Chronic endocarditis of all the valves.
Mitral, aortic and tricuspid stenosis and regurgitation.
Chronic fibrous pericarditis.
Congestive heart failure; left hydrothorax; ascites.
Acute central necrosis of the liver.
Nephrosis (Fahr).
Bronchopneumonia.
Organizing pneumonitis.
Pulmonary collapse, left lower lobe.
Syphilitic aortitis.
Neurosyphilis.
Fibrous pleuritis, left.

PATHOLOGIC DISCUSSION

DR. MALLORY: We found at autopsy a huge heart weighing 900 grams, with dilatation and hypertrophy of both sides which impressed the prosector as being more marked on the left than on the right, although I think the measurements fail to bear that out, since the right heart musculature measured 6 millimeters in thickness, certainly more than fifty per cent greater than normal, and the left about 16 millimeters, which is only slightly greater than normal. There were very marked old calcareous lesions of the mitral valve, which was so narrow that it barely admitted a fingertip. The aortic valve showed definite stenosis and insufficiency with interadherent cusps and a completely fixed valve that could not possibly have closed. The tricuspid valve also showed some lesions, so that as far as the heart is concerned it looks like a case of pure rheumatic heart disease.

When we came to the aorta we found a calcified area, markedly thickened, in the ascending aorta beginning four centimeters above the valve and running up for five centimeters more. The intima throughout the rest of the aorta showed little or no sclerosis. In this one region the intima was thickened to two millimeters or more. There were no definite scars, no dilatation, no tree barking. We were not able in gross to make a diagnosis of luetic aortitis and thought that it was more probably a localized area of rheumatic aortitis than of luetic. The sections, however, prove without much question that it was luetic in character. In the past two years we have learned that rheumatism can produce a much more severe grade of aortitis than we previously believed, and I think in the past a number of our diagnoses of luetic aortitis have been incorrect. They were actually cases of rheumatic aortitis, more marked than we had supposed was possible. I do not believe that anyone knows definitely enough the possible extent of rheumatic damage to be dogmatic about these cases; but the localized areas of complete destruction of the media with intense lymphocytic infiltration such as you see at this point are entirely characteristic of an active acute luetic lesion and are not those that are ordinarily described in a rheumatic process, so that I feel reasonably certain that the aortic lesion in this case is luetic.

We have in this case proof of an active luetic process not only serologically but from the postmortem findings in the brain, about which Dr. Kubik will tell us.

DR. CHARLES S. KUBIK: On examination of the brain there were found changes in the ependyma, so-called ependymal granulations, which are typical of syphilis. In the gross specimen the ependymal surface has a granular appearance, like a shark's skin. Microscopically one finds small elevations of the surface with destruction of the ependymal cells and proliferation of fibrous glia. The fibrous glia protrudes through the defects in the ependyma and, it would seem, spreads out over the surface, in this case the floor of the fourth ventricle. Finally whatever ependymal cells remain are buried

under a layer of very dense fibrous glia which forms the lining of the ventricle. Here we have further evidence of syphilis, slight lymphocytic infiltration of the pia arachnoid and of the perivascular spaces of the brain and medulla. There are no other changes in the cortex which would be at all suggestive of general paralysis.

The spinal cord is grossly negative and myelin stains reveal no degeneration of the posterior columns.

With these findings one can make a positive diagnosis of syphilis of the central nervous system. The process however seems to be a mild one. It has probably been present for many months, very likely for a number of years. It also seems to have run a mild course clinically, probably because important structures were not seriously affected.

CASE 19372

AN UNUSUAL GASTRIC LESION

Surgical Department

Presentation of Case

Dr. Champ Lyons:* This is the case of a sixty-one year old married ex-janitor.

We first saw him in the Outpatient Department three years before he entered the wards. At that time he complained of weight loss of eighteen months' duration and anorexia. His urine gave an orange test for sugar and he was considered a diabetic. No blood sugar studies are recorded. On a diet containing 1200 calories a day he managed to go along without insulin, and had no further symptoms until three months before entry, when he noticed gradually increasing constipation, flatulence, anorexia and easy fatigue. He lost 25 pounds in the six months prior to entry. He was studied at a Boston hospital under a special technic which involved careful manipulation with a small amount of barium in the stomach. The rugae were outlined and a small concave defect was demonstrated in the wall of the stomach. He was referred to this hospital for study.

Here we found that he had no anemia. Dr. Hunter examined the blood and found no adequate basis for a diagnosis of lymphoma. A medical consultant felt that the presence of diabetes was not attributable to cirrhosis of the liver. A Hinton test was negative. Gastric analysis showed 90 units of free acid after the introduction of ergamin, normal free acid following alcohol. The stools showed no blood at any time.

Repeated films were done in the X-ray Department.

Dr. William C. Martin: The stomach shows a three centimeter concave defect on the lesser curvature with no definite involvement of the mucous membrane. It would roll under the fingers and it moved with the stomach, showing that it was in the stomach wall and not due to external pressure.

Dr. Lyons: On the twelfth day operation was done. The patient's postoperative course was extremely even. The temperature rose to 101° the day after operation. After that time it was above normal on only one occasion. He was put on the régime which we give surgical patients. The stomach filled up rather readily, but other than that he had no discomfort of any kind. Three weeks after operation he was discharged improved.

*Senior interne on the West Surgical service.

Clinical Discussion

Dr. Lyons: At the Massachusetts General Hospital a diagnosis of mural tumor of the stomach was made.

At operation the findings agreed with those of the X-ray Department. A small tumor was found and a posterior gastro-enterostomy was done.

Dr. George A. Leland: At operation, which was done under avertin and ether, when the incision was made through the peritoneum he strained slightly and the stomach appeared in the wound. On the lesser curvature was a little tumor. It was intramural. The serosa seemed to glide over the surface. It felt exactly like an endometrial fibroid.

Pathologic Discussion

Dr. Tracy B. Mallory: The specimen in this case is here and is a very typical one grossly for either leiomyoma or fibroma of the stomach. I do not believe it would be possible to tell from the gross examination which it was. With the sections and various differential stains it is usually possible to decide between these two, though sometimes it is difficult even then. In this case we feel quite confident that it is fibroma of perineurial origin. You perhaps remember that fibromas arising from nerve sheaths often show very marked whorls. In one case of perineurial fibroma of the stomach we had recently the whorls were so obvious that they could be made out in gross.

From the general literature on benign tumors and on sarcomata of the stomach one would gather that smooth muscle tumors are very much commoner than fibromata. I have recently begun to be a little skeptical of that, we have had such a considerable number of them that are definitely fibromatous in character.

This present case of Dr. Leland's is growing with considerable rapidity and seems to have enough mitotic figures so that we had to classify it as sarcoma. On the other hand it is well circumscribed, and I think the probability of metastasis is extremely slight. Almost certainly the man has been cured.

Dr. Jones, you have probably seen more of these cases than any of us. Do you care to say something about them?

DR. DANIEL F. JONES: I am sorry to say that I have never operated upon a benign tumor of the stomach.

DR. J. H. MEANS: Have you any idea as to what the proportion of benign tumors of the stomach is to malignant ones?

DR. MALLORY: It would be very distinctly under one per cent; I suppose it would be under half of one per cent.

DR. GEORGE W. HOLMES: Is it not rather difficult to get reliable statistics? These benign tumors must become malignant when let alone, and when they reach you many of them may have reached this stage.

DR. MALLORY: Very minute benign tumors of the stomach have been found in considerable numbers at the Mayo Clinic. They looked through the stomach in several hundred successive autopsies hunting for very minute myomata and found them in twelve per cent of all cases. The vast majority of these tumors would have been missed in any ordinary postmortem examination. It was only by running every inch of the stomach through the fingers that they were able to detect them. The diagnoses were later confirmed histologically; there was no question that they were dealing with myomata. Nevertheless myomata of significant size are rather uncommon. It is very seldom that they reach a diameter as great as half a centimeter. A tumor of that size would rarely be missed. We do not find these in more than about two per cent of our autopsies, I should say.

DR. HOLMES: I suppose we are seeing more of these cases now because of the introduction of the method of examination advocated by Berg of Germany, and the use of a very small barium meal in the study of the stomach mucosa. His work is based on the earlier work of Forssell, who studied the normal mucosa. The principal idea of Berg's technic is the use of a small compression diaphragm which he fixes on the fluoroscopic screen and when the area to be studied is located he takes the picture with pressure maintained. His technic is of great value in the diagnosis of early lesions, and is the method used at the Boston Dispensary by Dr. Ettinger, who was one of Berg's pupils.

DR. MALLORY: I think there is every reason to believe, as Dr. Holmes said, that many of these tumors may run along at a very slow rate for a considerable time and then rather suddenly start growing, and that consequently very careful fluoroscopic and x-ray examinations are extremely important in picking up these cases at a stage where they are still curable by operation.

DIAGNOSIS

Fibrosarcoma of the stomach, neurogenic in origin.

The New England
Journal of Medicine

SUCCESSOR TO
THE BOSTON MEDICAL AND SURGICAL JOURNAL

Established in 1828

Published by THE MASSACHUSETTS MEDICAL SOCIETY under the jurisdiction of the

COMMITTEE ON PUBLICATIONS

R. I. LEE, M.D., *Chairman* HOMER GAGE, M.D.
R. B. OSGOOD, M.D. R. M. SMITH, M.D.
F. H. LAHEY, M.D.

EDITORIAL STAFF

REID HUNT, M.D. STEPHEN RUSHMORE, M.D.
JOHN P. SUTHERLAND, M.D. HANS ZINSSER, M.D.
GEORGE R. MINOT, M.D. BENJAMIN WHITE, PH.D.
FRANK H. LAHEY, M.D. HENRY R. VIETS, M.D.
SHIELDS WARREN, M.D. ROBERT N. NYE, M.D.
GEORGE L. TOBEY, JR., M.D. ROBERT M. GREEN, M.D.
C. GUY LANE, M.D. CHARLES C. LUND, M.D.
WILLIAM A. ROGERS, M.D.

WALTER P. BOWERS, M.D., *Managing Editor*

ASSOCIATE EDITORS

GEORGE G. SMITH, M.D. WILLIAM B. BREED, M.D.
JOSEPH GARLAND, M.D.

THE NEW HAMPSHIRE MEDICAL SOCIETY
PUBLICATION COMMITTEE

O. E. SULLIVAN, M.D. H. H. AMSDEN, M.D.
R. H. MARCOTTE, M.D.

THE VERMONT STATE MEDICAL SOCIETY
PUBLICATION COMMITTEE

WILLIAM G. RICKER, M.D. C. F. DALTON, M.D.
E. A. STANLEY, M.D.

SUBSCRIPTION TERMS: *$6.00 per year in advance, postage paid for the United States, Canada $7.04 per year, $8.52 per year for all foreign countries belonging to the Postal Union.*

Material for early publication should be received not later than noon on Saturday. Orders for reprints must be sent to the Journal office, 8 The Fenway.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to The New England Journal of Medicine, 8 The Fenway, Boston, Mass.

BOSTON'S LEAD POISON PROBLEM

THE condition of a patient in the Children's Hospital in Boston recently led to repeated x-ray examination of this child. It was found that there was an increasing density of the extremities of the long bones and the question of lead poisoning was raised by the roentgenologist. The case was reported to the State Department of Public Health and an examination of the water supply of the house in Dorchester in which this patient lived was requested. The facts found were that the connection to the street water main was by a one-inch lead pipe approximately one hundred feet long, with house service of brass pipe. An analysis of the water standing in the pipe of this house overnight showed a lead content greater than that which is known to cause lead poisoning. Substitution of cement-lined pipe for the lead pipe was recommended.

More or less general conditions in Boston relating to the use of lead pipe are disconcerting, because it was the custom in earlier years to make house connections to street water mains by lead pipe and the Deputy Commissioner of the City Health Department has informed the *Journal* that many of these connecting lead pipes still exist. Further, that analyses of water from various localities in Boston have demonstrated the presence of lead to an objectionable degree.

Standing water in the house in which the case cited had lived showed .0657 parts of lead to 100,000 of standing water with .0314 parts in running water. Other samples of water supplied to the city of Boston show about the same proportion of lead, the highest proportion being 0.114 to 100,000 parts of water.

Two systems of water supply to Boston are employed, a high and a low pressure system. A sample of water taken from a house supplied by the high pressure system showed 0.124 parts of lead per 100,000 and the supply contained free chlorine.

The Deputy Commissioner of Health of Boston states that "the water which most of the people of Boston are drinking contains an amount of lead which cannot be ignored. Furthermore, the amount may be increased because the action of the chlorine in water is to dissolve in the old lead water main connections the protective coating which was built up before the water was chlorinated. At present new water main connections are copper pipes, but a very small proportion of buildings in Boston have such connections."

The danger of the use of lead pipe for conducting drinking water has been "confirmed by the United States Public Health Service in a communication received from Surgeon General Cumming under date of July 11" by the Boston Health Department. In a reprint of the United States Public Health Reports of July 28, 1922, a summary is given which states, "No water to be used for drinking purposes should contain lead compounds in a quantity greater than what would correspond to a half a part of lead per million of water. Lead to the extent of 0.025 per 100,000 is sufficient to condemn a potable water and 0.36 parts per 1,000,000 may be poisonous."

The Deputy Commissioner further has stated in his report that "We are finding in Boston water from 0.60 to 1.14 parts of lead per million of water. This amount certainly justifies the statement that the amount of lead in Boston water is near the danger point and that a comparatively small increase would bring it up to an amount which has been known to cause wholesale symptoms of poisoning from a public water supply.

"The susceptibility to lead poisoning varies greatly in different individuals. Some persons have a much greater capacity to eliminate lead from their bodies than other persons. The dan-

ger of poisoning also depends on the individual's daily consumption of water and the period for which such consumption is continued.

"Perhaps we might get by with the present amount of lead in Boston water for a while without serious consequences, but certainly if the chlorination of the supply is to be continued the replacement of the present lead water main connections by some other material is the price which the people of the city will have to pay in the interest of their health."

Unfortunately it is known that there are other sources of lead in the atmosphere of a city, part of which now is contributed by the exhaust from automobiles, and, since lead is a cumulative poison, careful studies by competent chemists seem to be in order to determine whether there is now or in prospect a definite lead hazard to health in Boston.

THE WEAKEST LINK IN OUR WARFARE AGAINST TUBERCULOSIS

THE Central New England Sanatorium, Inc. and Industrial Colony, Rutland, Massachusetts, uses the words in the heading above for its slogan in a campaign to raise money to enable it to carry on its work.

This weakest link is described as the omission of plans and arrangements for preparing the sanatorium patient to resume his normal life after the institutional treatment has brought arrest or all possible improvement of the disease. The warning is plainly emphasized that discharged patients too often are projected into home life without any power of adaptation to uncontrolled activity and too often ambition or necessity drives one to more exacting labor than the damaged body can maintain. This may mean too many hours or a load beyond safe limits with the result that the sanatorium treatment must again be employed and perhaps repeated several times. This may be so disheartening that the victim may lose all hope and resign himself to the progress of his disease. Even if repeated terms in the sanatorium may finally bring a cure, which is unlikely, the economic problem is of great importance. A cure or radical improvement is too valuable to be jeopardized.

In a concise way the plans of the Central New England Sanatorium and Industrial Colony are set forth in the early pages of a brochure which is an appeal for financial support and are as follows:

"'*Future advances in the conquest of tuberculosis will be mainly along economic lines.*'"

"*The weak point* in the modern treatment of tuberculosis is the failure to provide for a *gradual* return to normal working life after the sanatorium rest régime.

"*Bridging the gap* from rest régime to active self-support without the usual relapses is the next step in the conquest of the disease.

"*The Industrial Colony* of the Central New England Sanatorium provides the means for patients to regain gradually their working and earning power while under careful medical supervision.

"*Work with wages* is provided in some thirty occupations in keeping with the patient's needs, and vocational training is available where a new trade must be learned to fit individual handicaps.

"*It is better business* to cure the patient once, and to provide him with the means for self-support within his limitations than to cure him partially over and over again.

"*This pioneer Industrial Colony* has put into successful practice an idea in gainful and reconstructive employment which cannot but advance the treatment of tuberculosis everywhere. The highest medical authorities approve it.

"*This combination of Sanatorium and Industrial Colony* must continue to be subsidized as an institution leading the advance in tuberculosis technique.

"*The battle with tuberculosis* is not yet won. Despite amazing progress, 25,000 people in Massachusetts have tuberculosis today, and at least 800,000 people the country over are still tuberculous.

"*The future of this institution* is rich in possibilities: it is a place where treatment can be demonstrated; its work is available to the medical profession for observation; to medical students for intensive study; and to highly trained graduate students for research investigation."

The work of the Sanatorium is endorsed by Dr. Livingston Farrand, Dr. Lawrason Brown and Dr. George H. Bigelow.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

JOSLIN, ELLIOTT P. A.B., Ph.B., M.A. (Hon.), M.D. Harvard University School of Medicine 1895. Director George F. Baker Clinic, New England Deaconess Hospital. Clinical Professor of Medicine, Harvard Medical School. His subject is "Fat and the Diabetic." Page 519. Address: 81 Bay State Road, Boston.

SHEDDEN, WILLIAM M. A.B., M.D. Harvard University Medical School 1920. F.A.C.S. Assistant Surgeon to Outpatients and Chief of Rectal Division, Tumor Clinic, Massachusetts General Hospital. Chief of Tumor Clinic, Boston Dispensary. His subject is "Carcinoma of the Rectum and Sigmoid With Particular Reference to the Disease as Seen In Youth." Page

528. Address: 270 Commonwealth Avenue, Boston.

THURMON, FRANCIS M. B.S., M.D. Harvard University School of Medicine 1926. Physician-in-Chief, Department of Dermatology and Syphilology, The Boston Dispensary. Assistant Professor in Dermatology, Tufts College Medical School. Physician in Dermatology, The Boston Floating Hospital. Address: 520 Commonwealth Avenue, Boston. Associated with him is

TOLMAN, MAURICE M. A.B., M.D. Harvard University School of Medicine 1927. Assistant in Dermatology and Syphilology, Massachusetts General Hospital. Assistant Physician, Department of Dermatology and Syphilology, The Boston Dispensary. Assistant Dermatologist, Beth Israel Hospital. Consultant in Dermatology to the Lowell General Hospital, Lowell, Mass. Assistant in Dermatology and Syphilology, Tufts College Medical School. Address: 353 Commonwealth Avenue, Boston. They write on "Acquired Hypersensitivity to the Arsenobenzol Radical of Bismarsen." Page 540.

ERNSTENE, A. CARLTON. M.D. State University of Iowa College of Medicine 1925. Assistant in Medicine, Beth Israel Hospital; Faculty Instructor in Medicine, Harvard Medical School, Boston. Address: Cleveland Clinic, Cleveland, Ohio. Associated with him is

RISEMAN, JOSEPH E. F. M.D. Harvard University School of Medicine 1929. Resident Physician, Beth Israel Hospital. Assistant in Medicine, Harvard Medical School. Teaching Fellow in Medicine, Tufts College Medical School. Address: 330 Brookline Avenue, Boston. Their subject is "Endemic Typhus Fever in Boston. A Report of Ten Cases." Page 542.

HANFLIG, S. S. A.B., M.D. Harvard University Medical School 1927. Assistant Orthopedic Surgeon to the Outpatient Department, Beth Israel Hospital. Clinical Assistant Orthopedist, Outpatient Department, Cambridge Hospital. His subject is "Familial Congenital Dislocation of the Hip." Page 545. Address: 371 Commonwealth Avenue, Boston.

MATZ, PHILIP B. M.D. Long Island College of Medicine 1908. Chief, Research Subdivision, Medical and Hospital Service, Veterans Administration, Washington, D. C. His subject is "Clinical and Economic Features of Arthritis in Ex-Members of the Military Service." Page 547. Address: Arlington Building, Washington, D. C.

MISCELLANY

"DAMAGED LIVES"

The Massachusetts Society for Social Hygiene desires to call attention to the forthcoming production of the motion picture drama "Damaged Lives" which will open at the Majestic Theatre, Boston, September 15, in the premiere showing in the United States.

The picture visualizes, in graphic but tactfully handled scenes and dialogue, the story of a young married couple who become infected with syphilis, and their fight toward health and happiness.

"Damaged Lives" is not a sex picture, but a wholesome dramatic production, conveying a moral and health lesson which every one should learn. It has been produced with such care that it can offend no one. It will be advertised with dignity and without any sensational or salacious appeal.

The drama will be followed by an interesting sound film presenting authentic information concerning the venereal diseases. This film has been prepared by the American Social Hygiene Association, under whose auspices both the picture and lecture are to be shown.

No one under sixteen years of age will be admitted.

All physicians are urged to see the film.

MORTALITY RATES

Telegraphic returns from 85 cities with a total population of thirty-seven million for the week ending August 26, indicate a mortality rate of 9.0 as against a rate of 9.4 for the corresponding week of last year. The highest rate (15.0) appears for Knoxville, Tenn., and the lowest (5.1) for Waterbury, Conn. The highest infant mortality rate (14.7) appears for Tampa, Fla., and the lowest for Bridgeport, Conn., Canton, Ohio, Dayton, Ohio, Des Moines, Iowa, Duluth, Minn., Erie, Pa., Fort Wayne, Ind., Omaha, Neb., Schenectady, N. Y., Spokane, Wash., and Wilmington, Del., which reported no infant mortality.

The annual rate for 85 cities is 11.1 for the thirty-four weeks of 1933, as against a rate of 11.4 for the corresponding period of the previous year.

SUMMARY OF DEATHS AND DEATH RATES (ANNUAL BASIS) FROM AUTOMOBILE ACCIDENTS PER 100,000 ESTIMATED POPULATION FOR 86 CITIES FOR CORRESPONDING PERIODS OF 1933 AND 1932

	Week ending		First 34 weeks	
	Aug. 26, 1933	Aug. 27, 1932	1933	1932
Total deaths	149	147	4,799	4,860
Death rate	20.8	20.9	19.7	20.3

CORRESPONDENCE

FELLOWSHIPS FOR POSTGRADUATE STUDY

Harvard University
Medical School
Courses for Graduates

September 12, 1933.

Editor, *New England Journal of Medicine*,

An announcement was made, early in the sum-

mer, in the correspondence column of this *Journal*, to the effect that the Commonwealth Fund of New York was offering to Fellows of the Massachusetts Medical Society, fellowships for post-graduate study at the Harvard Medical School, Courses for Graduates.

The Commonwealth Fund has awarded fellowships to the following doctors:

Ira M. Dixson, Stockbridge.
Daniel H. Hiebert, Provincetown.
Howard B. Marble, Shelburne Falls.

A few of these fellowships are still available for Fellows of the Society who have been in practice at least five years, and who are located in towns of under ten thousand population.

Information may be obtained from the Commonwealth Fund, 41 East 57th Street, New York City, or from the Assistant Dean of the Courses for Graduates, 240 Longwood Avenue, Boston.

Yours very truly,
LEROY E. PARKINS,
Secretary to the Courses for Graduates
under the Commonwealth Fund.

ENDORSEMENT OF THE NRA

Cambridge Tuberculosis and Health Association
689 Massachusetts Avenue, Room 305
Cambridge, Mass.

Editor, *New England Journal of Medicine*,

The enclosed news item may be of some interest, as so far as I know, we are the first health organization to join the NRA.

The Associated Press has used the article through New England and New York.

Sincerely yours,
MABEL GREELEY SMITH,
Executive Secretary.

September 7, 1933.

NRA UPHELD AS IMPORTANT TO HEALTH RECOVERY PROGRAM

Cambridge Tuberculosis and Health Association, one of oldest in Country — writes President Roosevelt offering services and coöperation as member of NRA

Cambridge, Mass., Sept. 5—The Cambridge Tuberculosis and Health Association, one of the oldest organized health associations in the country, has joined the NRA campaign, and its president, Dr. Hilbert F. Day, has sent the following letter to President Roosevelt:

"Because this Association believes that the NRA has as its purpose the rehabilitation of the American home, and because an adequate earned income is vital to the maintenance of the health of the family, the Cambridge Tuberculosis and Health Association, one of the oldest health organizations in the United States, established in 1902, has joined the NRA.

"Our purpose has always been to further the principles and ideals of family security and welfare advocated by Secretary Frances Perkins in her radio address in Boston last night. For upwards of thirty years we have striven to promote the health and well-being of the family, and especially to protect the children who have been exposed to unusual health hazards. Recent experience has shown how greatly these hazards are increased by unemployment and by conditions due to industrial inactivity.

"The Association therefore welcomes this opportunity to offer its services and coöperation to you, as President of the United States, in your magnificent effort to rehabilitate family life and thus restore a standard of living that is essential to the health of the American people."

(Signed) HILBERT F. DAY, M.D., *President.*
Cambridge Tuberculosis and
Health Association.

A TRIBUTE TO MISS ANNIE MCDOWELL

Fairfax Hall, Harvard Square,
Cambridge, Mass.,
September 11, 1933.

Editor, *New England Journal of Medicine*,

It is with much sadness that I have learned of the recent death of Miss Annie McDowell, former Superintendent of Nurses at Johns Hopkins Hospital, and the Newton Hospital. Miss McDowell died at Baltimore, Maryland, on August 29.

Miss McDowell was early associated with the foundation of Johns Hopkins Hospital, where she was a pioneer in the creation of the Training School for Nurses at that institution. Later she was Superintendent of Nurses at the Newton Hospital, Newton, Massachusetts.

Retiring from her position as Superintendent of Nurses, she opened a small private hospital on Newbury Street, Boston, where for many years she served the medical profession of greater Boston. Advancing years made her give up active nursing and she discontinued her hospital to retire to private life at Cambridge, Mass.

Retirement did not mean that she lost interest in the sick or afflicted,—in Cambridge she sought out at Phillips House, Harvard University, a blind law student to whom she gave many hours of gratuitous service in reading from his textbooks, and a similar service she gave to a blind woman of Cambridge, who was a shut-in, and benefited from this thought also.

Her neighbors in Cambridge also knew the thought and solicitude she had for their welfare; for she was always, with her sister, Miss Sarah McDowell, also a nurse, the first to call and offer assistance in case of illness. She, on occasion, would show the new mother the care and handling of a new baby, and one of these babies grew up

to be a source of much pleasure and interest to these sisters.

The illness of another sister necessitated her removal to Baltimore, where she nursed her sister back to health again. Here at Baltimore she had an opportunity to renew many of the old associations formed at Johns Hopkins Hospital; until stricken with a heart condition, that confined her to her home.

As a friend and neighbor, who in a serious illness, knew her personal interest and kindness, I would pay tribute to this noble and fine woman, who exemplified during her whole professional life the true nurse and woman. I regret her passing, as I feel the world has lost a noble soul.

Sincerely yours,

DAVID H. GIBSON, M.D.

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHARMACY AND CHEMISTRY

535 North Dearborn Street, Chicago, Ill.,
August 31, 1933.

Managing Editor,
The *New England Journal of Medicine,*

In addition to the articles enumerated in our letter of August 2 the following have been accepted:

U. S. Standard Products Company

Antimeningococcic Serum Polyvalent, 30 cc. vial package

Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 10 cc. vial package

Rabies Vaccine—U.S.S.P. (Semple Method) 7 syringe packages

Rabies Vaccine—U.S.S.P. (Semple Method) 14 vial packages

Yours very truly,
PAUL NICHOLAS LEECH, *Secretary,*
Council on Pharmacy and Chemistry.

RECENT DEATH

ROBINSON—FREDERICK HILLIARD ROBINSON, M.D., of 31 7th Street, New Bedford, Massachusetts, died in the Huggins Hospital, Wolfeboro, New Hampshire, August 31, 1933. He was born in Pittsfield, New Hampshire, October 5, 1868. He graduated from the Tufts College Medical School in 1896 and practiced in New Bedford for many years. He had been in ill health for nearly a year.

He joined the Massachusetts Medical Society in 1925.

He is survived by a widow, two sons and a sister.

NOTICE

MAURICE O. BELSON, M.D., announces the opening of an office at 485 Commonwealth Avenue, Boston.

NOTICES OF MEETINGS

THE AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

1933 CONVENTION, BOSTON

The Thirty-Eighth Annual Convention of The American Academy of Ophthalmology and Otolaryngology will be opened by a meeting in the Ballroom of the Hotel Statler, September the seventeenth, at five-thirty P.M. The following program will be held:

Dr. Burt R. Shurly, President, Presiding.

1. Address of Welcome. Hon. James M. Curley, Mayor of Boston.
2. "Cultural, Spiritual and Material Medicine." Dr. Edward H. Cary, Dallas, Texas.
3. "Concerning Eyestrain." Dr. Edward Jackson, Denver, Colo.
4. "Facts and Fallacies About the Home Use of Eye Remedies." Dr. W. L. Benedict, Rochester, Minn.
5. "Colds—What They Can Do to Our Ears and Our Brain." Dr. Wells P. Eagleton, Newark, New Jersey.

Physicians, medical students and nurses are cordially invited to attend.

NEW ENGLAND SURGICAL SOCIETY

The Annual Meeting of the New England Surgical Society will be held September 29 and 30, 1933, at Boston, Mass.

The tentative program is as follows:

Friday, September 29: A.M., Clinics; P.M., Scientific Session; Evening, Annual Dinner.

Saturday, September 30: A.M., Scientific Session; 1 P.M., Annual Meeting.

SCIENTIFIC PAPERS, FRIDAY AFTERNOON, SEPTEMBER 29

1. "Carcinoma of the Small Intestine." Dr. Horace K. Sowles.
2. "Operative Management of Cancer of the Rectum." Dr. Frank H. Lahey.
3. "Cancer of the Breast. End Results; Massachusetts General Hospital, 1921-1922-1923." Dr. Robert B. Greenough, Dr. Grantley W. Taylor, Dr. Charles Dumas—By Invitation.
4. "Cancer of the Breast. End Results; Massachusetts General Hospital, 1924-1925-1926." Dr. Channing C. Simmons, Dr. Grantley W.

Taylor, Dr. Richard H. Wallace—By Invitation.

5. "Regional Ileitis; a Clinical, not a Pathological Entity." Dr. John Homans, Dr. George M. Hass—By Invitation.

6. "Abdominal Symptoms with or without Abdominal Lesions in Diabetic Acidosis." Dr. Leland S. McKittrick.

7. "Spontaneous Rupture of the Stomach During Labor." Dr. James Raglan Miller.

SCIENTIFIC PAPERS, SATURDAY MORNING, SEPTEMBER 30

1. "The Diagnosis and Treatment of Acute Sub-Dural Haematomata." A Report of 34 Cases. Dr. Donald Munro.

2. "Notes on Giant Cell Tumors of Bone." Dr. Frederic Jay Cotton.

3. "A Study of Two Hundred and Thirty-six Compound Fractures Treated at the Massachusetts General Hospital." Dr. Ernest M. Daland.

4. "Rupture of the Intervertebral Disc." Dr. William Jason Mixter, Dr. Joseph Barr—By Invitation.

5. "Compression Fractures of the Vertebral Bodies." Dr. John P. Bowler, Dr. John F. Gile.

6. "Appendices Epiploicae." Dr. Daniel C. Patterson.

7. "Suppurative Thyroiditis." Dr. Robert C. Cochrane.

BRISTOL NORTH DISTRICT MEDICAL SOCIETY

The fall meeting of the Bristol North District Medical Society will be held Thursday, September 21, at the Bristol County Tuberculosis Hospital, Attleboro, at 1 P.M.

PROGRAM

1 P.M. Dinner. Assessment $1.00.

2 P.M. Speaker: Dr. Arial W. George, Boston.

C. B. KINGSBURY, *Secretary.*

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

September 16—The American Board of Otolaryngology will hold an examination in Boston just prior to the meeting of the American Academy of Ophthalmology and Otolaryngology. Prospective applicants for certificate should address the Secretary, Dr. W. P. Wherry, 1500 Medical Arts Building, Omaha, Nebraska.

September 17—The American Academy of Ophthalmology and Otolaryngology. See page 563.

September 17 to 24—Microscopic, Oral Cavity, and Bone Diagnostic Demonstration of Cancer, at the Mayflower Hotel, Washington, D. C.

September 19, 20, 21—The Connecticut Clinical Congress will meet at New Haven. Subjects for consideration: Diseases of the Blood, Diet in Disease, Industrial Injuries and Neuroses. Lectures, Demonstrations, Group Conferences.

September 25-30—The American Congress of Radiology will be held at the Palmer House, Chicago. For particulars write to Dr. Benjamin H. Orndoff, 2561 North Clark Street, Chicago.

September 29 and 30—New England Surgical Society at Boston. See page 563.

October 9-12—The American Public Health Association will hold its sixty-second annual meeting at Indianapolis. For details on the scientific program write to the American Public Health Association, 450 Seventh Avenue, New York, N. Y.

October 9-13—The Clinical Congress of the American College of Surgeons will hold its twenty-third annual session at Chicago. Headquarters for the Congress will be at the Stevens Hotel.

October 13, 1933 - May 11, 1934—William Harvey Society. (Eight Lectures. Monthly.)

October 16, 17, 18—Massachusetts State Nurses' Association, Hotel Kimball, Springfield, Mass. For details write Helene G. Lee, R.N., 420 Boylston Street, Boston.

October 18—New England Physical Therapy Society. First Fall Meeting. Detailed announcement later. Dr. Arthur H. Ring, Secretary, 163 Hillside Avenue, Arlington, Mass.

October 23 - November 3—The 1933 Graduate Fortnight of the New York Academy of Medicine. The theme during the two weeks of intensive study will be Metabolic Disorders. A complete program may be obtained by writing Dr. Frederick P. Reynolds, The New York Academy of Medicine, 2 East 103rd Street, New York City.

October 25-30—International Congress on the Scientific and Social Contest Against Cancer will be held at Madrid. For information address Dr. Julio Bejarano, Atocha, 104. Madrid, Spain.

October 28—The American Board of Dermatology and Syphilology will hold written examinations for candidates in the following cities: New York City; St. Louis, Mo.; Boston, Mass.; Cleveland, Ohio; San Francisco, Calif.; Philadelphia, Pa.; Chicago, Ill. Information may be obtained from the Secretary, Dr. C. Guy Lane, 416 Marlborough Street, Boston, Mass.

December 15 and 16—The American Board of Dermatology and Syphilology will hold oral examinations in New York City. Information may be obtained from the Secretary, Dr. C. Guy Lane, 416 Marlborough Street, Boston, Mass.

April 16-20, 1934—The American College of Physicians will hold its Eighteenth Annual Clinical Session in Chicago at the Palmer House. For information write Mr. E. R. Loveland, Executive Secretary, 133-135 South 36th Street, Philadelphia, Pa.

July 24-31, 1934—The IVth International Congress of Radiology will be held in Zurich under the presidency of Professor H. R. Schniz. General Secretary Dr. H. E. Walther, Gloriastrasse 14, Zurich.

DISTRICT MEDICAL SOCIETY

BRISTOL NORTH DISTRICT MEDICAL SOCIETY

September 21—See notice elsewhere on this page.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

Schedule 1933-1934

Meetings will take place on November 8 at the Bear Hill Club, Stoneham; January 10 at Melrose; March (2nd Wednesday) at Wakefield, and May (2nd Wednesday) at Winchester.

ALLAN R. CUNNINGHAM, Secretary.
76 Church Street, Winchester, Mass.